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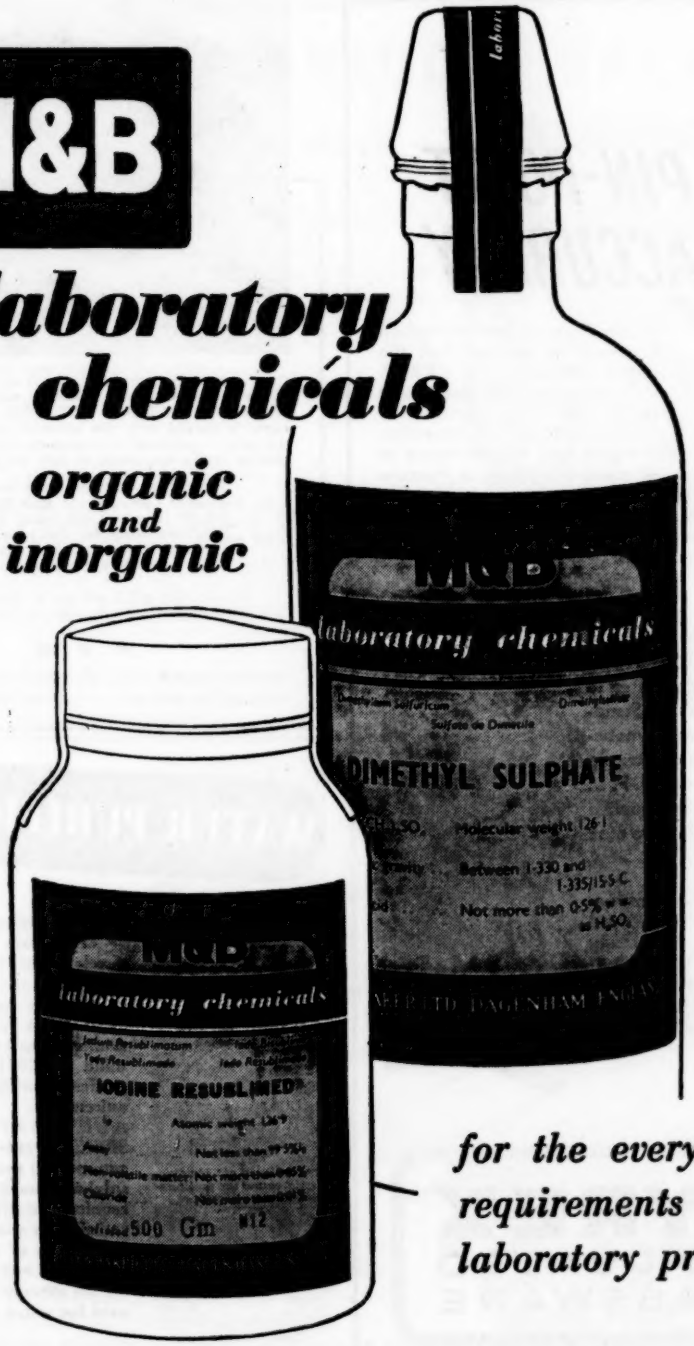

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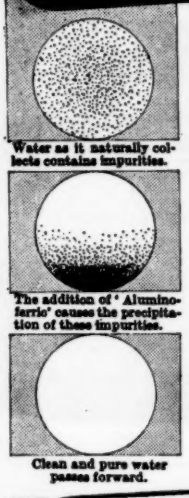

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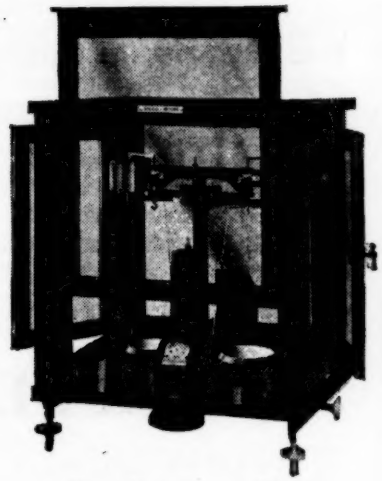

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QUARTERLY REVIEWS

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164. *Toxic Fluorine Compounds Containing the* C–F *Link. Part II. 2-Fluoroethanol and its Derivatives.*

By B. C. Saunders, G. J. Stacey, and I. G. E. Wilding.

A practicable method for the production of 2-fluoroethanol is described and an account is given of its highly toxic properties. A variety of compounds containing the 2-fluoroethyl group is described. The facile conversion of *fluoroethyl thiocyanate* into *fluoroethylsulphonyl chloride* has been effected. An example of the fluoroethylating action of 2 : 2′-*difluorodiethyl sulphate* is given.

In this work on compounds containing the C–F link, it was obviously desirable to prepare 2-fluoroethanol, both for toxicity tests on the compound itself, and as a starting material for the production of other fluorine compounds. Swarts (*Chem. Centr.*, 1914, I, 1551) was unable to obtain 2-fluoroethanol by the action of silver fluoride or mercuric fluoride on either ethylene chlorohydrin or ethylene bromohydrin. He obtained acetaldehyde in each case. He ultimately obtained fluoroethanol in very poor yield by the indirect method of hydrolysing fluoroacetin (from bromoacetin and mercuric fluoride) for 80 hours with dilute mineral acid.

In Report No. 3 on " Fluoroacetates and Allied Compounds " to the Ministry of Supply (March 31st, 1943) we described a very simple and efficient preparation of fluoroethanol (FEA) by heating together ethylene chlorohydrin and potassium fluoride in a rotating autoclave at 135° for 4 hours. Details of the method are described in the Experimental section. For large-scale work we found it advantageous to use nitrobenzene as a diluent, thereby enabling the reaction mixture to be stirred much more thoroughly and to render its removal (by suction or otherwise) from the autoclave more efficient.

Fluoroethanol is soluble in water and stable to moisture. As a lethal inhalant it produces convulsions in animals similar to those produced by methyl fluoroacetate (MFA). A concentration of 0·29 mg./l. (10 minutes' exposure) killed 62% of a batch of rabbits, guinea-pigs, and rats, and a concentration of 0·14 mg./l. killed 38%, all the deaths occurring within 12 hours. Mice were much more resistant, the L.C. 50 being about 1·1 mg./l.

1-Chloro-2-fluoroethane was found to be non-toxic. A concentration of 0·184 mg./l. failed to kill any animals whereas a similar concentration of fluoroethanol or of methyl fluoroacetate would have killed some 50% of a batch of rabbits, guinea-pigs, or rats. The chlorine atom in chlorofluoroethane was found to be very unreactive towards a variety of reagents, and this fact no doubt accounts for its non-toxic nature since it is unlikely that the animal body is able to hydrolyse it to the toxic fluoroethanol.

Under the conditions employed in our experiments no reaction occurred between chlorofluoroethane and potassium phthalimide or potassium thiocyanate. Magnesium (in ethereal suspension) did not react in the normal manner to give a Grignard reagent, although on prolonged heating, a certain amount of metal did go into solution to give a product which, on the addition of water, set to a jelly-like mass.

Attempts to prepare 2 : 2′-difluorodiethyl sulphide by the action of sodium sulphide on chlorofluoroethane resulted in the production of dithian together with other polymeric substances. Aniline either did not react at all or, under drastic conditions, gave *NN′*-diphenylpiperazine and *NN′*-diphenylethylenediamine.

Sodium phenoxide, however, reacted with chlorofluoroethane when they were heated together in alcoholic solution and gave *phenyl 2-fluoroethyl ether*, a solid which proved to be less toxic than MFA.

An attempt to prepare 1-bromo-2-fluoroethane by the partial fluorination of ethylene dibromide by means of antimony trifluoride was unsuccessful. The compound was best prepared by the action of phosphorus tribromide on FEA. Swarts (*Bull. Acad. roy. Belg.*, 1914, 7), who first prepared the compound by means of this reagent, poured the crude product into water, but he did not record the yield. Using his method, we obtained a 6% yield. We modified the method and were ultimately able to obtain consistent yields of about 50%. The compound was relatively non-toxic and the bromine atom rather unreactive, but considerably more reactive than the chlorine atom in chlorofluoroethane. For example bromofluoroethane was readily converted by means of potassium thiocyanate into *2-fluoroethyl thiocyanate*. As a lethal inhalant the toxicity of the thiocyanate was inferior to that of MFA. Toxicity by injection, however, appeared to be high. The results on this aspect of the work will be reported later.

The action of potassium cyanide on bromofluoroethane was examined, but under the conditions used, which were similar to those for the thiocyanate, no reaction took place.

By employing the method similar to that of Johnson and Douglass for converting SCN into SO_2Cl (*J. Amer. Chem. Soc.*, 1939, **61**, 381), fluoroethyl thiocyanate was readily converted by the action of chlorine water into *2-fluoroethylsulphonyl chloride*, a stable liquid. When small animals were exposed to the vapour at a concentration of 0·5 mg./l. for 10 minutes, irritation and lachrymation were caused, but there were no deaths and all the animals recovered.

2-Fluoroethyl xanthate, $F{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CS{\cdot}OEt$, was a yellow oil formed by the action of sodium xanthate on bromofluoroethane. The compound has an L.D. 50 of 50 mg./kg. for subcutaneous injection into mice, thus showing it to be considerably less toxic than MFA (Part I, *J.*, 1948, 1773).

The action of sulphuryl chloride on FEA was investigated, chiefly with a view to preparing *2 : 2′-difluorodiethyl sulphate*, a compound which was expected to have applications analogous to those of diethyl sulphate. The method at first tried was similar to that recommended by Kharasch *et al.* (private communication, 1943) for the preparation of 2 : 2′-dichlorodiethyl sulphate. In this process, 2-fluoroethanol was added slowly to an excess of cooled sulphuryl chloride, the only product isolated being, however, *2-fluoroethyl chlorosulphonate*, $Cl{\cdot}SO_2{\cdot}O{\cdot}CH_2{\cdot}CH_2F$. In the second experiment, conditions were reversed and sulphuryl chloride was added to slightly more than the theoretical quantity of FEA. The difluorodiethyl sulphate was obtained this time, but not in large yield.

On exposing animals for 10 minutes to 0·327 g./m.^{3} of the chlorosulphonate, irritation was observed and rats showed the same type of convulsions as with MFA. However, only 2/13 of a batch of rabbits, guinea-pigs, and rats died within 24 hours. The difluorodiethyl sulphate was non-irritant and less toxic.

2-Naphthyl 2-fluoroethyl ether was readily prepared by warming an alkaline solution of 2-naphthol with 2 : 2′-difluorodiethyl sulphate. Subcutaneous injection into mice of the propylene glycol solution showed that the compound had an L.D. 50 of approximately 60 mg./k. and was therefore much less toxic than MFA.

The reaction between FEA and manganese dioxide and sulphuric acid was investigated initially with a view to prepare the corresponding fluorinated acetal. It soon became apparent that the isolation of the hitherto undescribed *fluoroacetaldehyde* might be possible in this experiment, and accordingly attention was directed to that end. Evidence for the formation of fluoroacetaldehyde was obtained by the isolation of the *2 : 4-dinitrophenylhydrazone* from the aqueous distillate. This fluorine-containing aqueous distillate also gave most of the usual aldehyde tests (*e.g.*, silver mirror with ammoniacal silver nitrate, slow pink coloration with Schiff's reagent, etc.). Analyses showed that the amount of aldehyde present in the distillate was only about 7%, but by suitable means of concentration (see p. 776) it was possible to obtain in small quantities a liquid of b. p. 89—93° containing about 80% of the aldehyde. Further dehydration gave a liquid of b. p. 57—65°, but this polymerised rapidly on standing.

By analogy with chloral and monochloroacetaldehyde it is to be expected that fluoroacetaldehyde might readily form a hydrate, and it is not improbable that, in the liquid of b. p. 89—93°, it was present largely in this form.

Toxicity determinations by subcutaneous injection into mice of a sample containing 80% of the aldehyde gave an L.D. 50 of 6 mg./kg. As the L.D. 50 for MFA is also 6 mg./kg., the two compounds are equally toxic, molecule for molecule, allowance being made for the presence of 20% of water in the aldehyde. This degree of toxicity is thus exactly in accordance with expectation.

Experimental.

2-Fluoroethanol.—Anhydrous ethylene chlorohydrin (226 g.) and dry finely-powdered potassium fluoride (200 g.) were heated in a rotating autoclave at 130—135° for 4 hours. After cooling, the product was extracted with ether, care being taken to grind up any solid crust as completely as possible with the ether. The solid was filtered off, and the ethereal filtrate shaken with dry sodium hydrogen sulphite for at least 1 hour to remove crotonaldehyde (formed as a by-product). The solution was again filtered and the ether distilled off through an efficient 30″ fractionating column. The residue was then carefully distilled, and the fraction of b. p. 103·5—105·5° collected; yield 75 g. (42%), b. p. 103·5°. Aldehydes were shown to be absent in pure fluoroethanol by Schiff's reagent. 2-Fluoroethanol is a colourless, almost odourless liquid, miscible with water in all proportions (Found: F, 29·2. Calc. for C_2H_5OF: F, 29·7%); f. p. −43°, $d_4^{19°}$ 1·1150, $d_4^{15°}$ 1·1095, $d_4^{20°}$ 1·1040; vapour pressure 5·55, 14·3, and 40 mm. at 0°, 15°, and 30°, respectively.

Notes on the preparation. (*a*) Some crotonaldehyde is produced in the reaction and this has nearly the same b. p. as that of fluoroethanol. It is therefore necessary to remove the aldehyde with solid sodium hydrogen sulphite.

(*b*) About 250 c.c. of nitrobenzene could, with advantage, be added as a diluent in the above reaction. The crude product was then much more easily removed from the autoclave. This was particularly useful for large-scale runs, for the reaction product could then be poured as a slurry from the autoclave. It must be emphasised, however, that nitrobenzene is not a suitable diluent for all fluorinations of the

above type; for example, at the higher temperature required in the preparation of methyl fluoroacetate (Part I, *loc. cit.*) explosions are likely to occur when nitrobenzene is used as diluent.

(*c*) The yields obtained with sodium fluoride (in place of potassium fluoride) were very small.

(*d*) Zinc fluoride and antimony fluoride did not react to any appreciable extent to give the alcohol, when heated with ethylene chlorohydrin for several hours without an autoclave.

Derivatives.—Phenylurethane. A mixture of phenyl *iso*cyanate (1·2 g.) and FEA (0·64 g.) in dry light petroleum (25 c.c., b. p. 100—120°) was heated under reflux for 30 minutes, and filtered hot; an oil separated, and on standing in a refrigerator overnight this solidified, and when it was again dissolved in light petroleum and chilled, it again separated as an oil. The oil solidified to the colourless *urethane*, m. p. 36° (Found: N, 7·7. $C_9H_{10}O_2NF$ requires N, 7·9%).

1-*Naphthylurethane.* A mixture of 1-naphthyl *iso*cyanate (1·7 g.) and FEA (0·64 g.) in dry light petroleum was heated as above. The liquid was filtered hot and on cooling the *urethane* crystallised; recrystallised from light petroleum (b. p. 100—120°), it had m. p. 128° (Found: N, 6·04. $C_{13}H_{12}O_2NF$ requires N, 6·2%).

3 : 5-*Dinitrobenzoate.* A mixture of 3 : 5-dinitrobenzoyl chloride (2 g.) and FEA (2 g.) was heated on a water-bath for 30 minutes. On cooling, the product solidified and was recrystallised from warm alcohol (10 c.c.). The white 3 : 5-*dinitrobenzoate* recrystallised from alcohol in fine, elongated, rectangular prisms, m. p. 86° (Found: C, 41·8; H, 2·94. $C_9H_7O_6N_2F$ requires C, 41·9; H, 2·74%).

1-*Chloro*-2-*fluoroethane.*—Fluoroethanol (32·1 g., 0·5 mol.) was placed in a flask, and thionyl chloride (59·5 g., 0·5 mol.) added slowly down a reflux condenser. Heat was evolved at first, but external cooling was not necessary. After the addition was complete, the mixture was heated under reflux for 30 mins. in an oil-bath at 90°. It was then fractionated through a 50-cm. column, the fraction, b. p. 51—55°, being collected. This was shaken with aqueous sodium carbonate to remove hydrochloric acid and sulphur dioxide, and then dried (Na_2SO_4) and distilled; yield 18·2 g. (44%) (Found: Cl, 43·14. Calc. for C_2H_4ClF: Cl, 43·02%). The compound was proved to contain fluorine.

Reaction with aniline. A mixture of aniline (13·9 g., 0·15 mol.) and chlorofluoroethane (6·6 g., 0·08 mol.) was gently heated under reflux for 18 hours. Much solid separated, and the product was extracted with boiling benzene, and the solution filtered and allowed to stand. The solid (insoluble in water) which separated was recrystallised from aqueous alcohol and gave a solid, m. p. 65° (not sharp), free from chlorine and fluorine. This product was proved to be *NN'*-diphenylethylenediamine (m. p.s given in literature vary from 59° to 65°).

The benzene filtrate was evaporated and a white solid remained. This distilled at 236—240°/16 mm. and was recrystallised from chloroform–alcohol; m. p. 159—162°. This compound, which contained nitrogen but not fluorine, was *NN'*-diphenylpiperazine which has m. p. 164—165°, b. p. 230—235°/12 mm. Under less vigorous conditions than the above, very little reaction took place.

In another experiment aniline and chlorofluoroethane were heated together in a sealed tube at 200° for 2 hours, but complete breakdown to intractable material took place.

Non-reaction with silver cyanide. A mixture of silver cyanide (13·4 g.) and chlorofluoroethane (8·3 g.) was heated under reflux for 8 hours, but there were no signs of reaction and on distillation unchanged chlorofluoroethane was obtained.

Reaction with sodium phenoxide. The phenoxide was prepared from sodium (4·6 g., 0·2 mol.) in alcohol (75 c.c.), to which was added phenol (18·8 g., 0·2 mol.) also dissolved in alcohol (25 c.c.). The mixture was then evaporated to dryness under reduced pressure, and the residual white solid powdered and dried; yield 22 g.

A mixture of sodium phenoxide (11·6 g., 0·1 mol.) and chlorofluoroethane (8·3 g., 0·1 mol.), dissolved in alcohol (30 c.c.), was heated under reflux for 18 hours. After removal of the solid which separated, the alcohol was distilled off, and the residual oil poured into water. The suspension was extracted with ether, and the extract washed with aqueous sodium hydroxide and then with water, and dried ($CaCl_2$). After removal of the ether, the residue distilled at 97—98°/22 mm.; yield 3·4 g. (24·3%). On redistillation the *phenyl ether* came over at 92·5—93°/17 mm. and solidified to colourless crystals, m. p. 41—41·5° (Found: F, 13·0. C_8H_9OF requires F, 13·56%).

Bromofluoroethane.—To FEA (38·4 g., 0·6 mol.) contained in a flask placed in ice-water, phosphorus tribromide (57·2 g., 0·2 mol.) was added slowly down a reflux condenser. There was no vigorous reaction and the drops of phosphorus tribromide disappeared on shaking. The mixture was then heated in an oil-bath at 100° for 10 minutes and hydrogen bromide was copiously evolved. The product was fractionated, and the fraction of b. p. 71—90° was collected, washed with aqueous sodium carbonate solution, then with water, dried ($CaCl_2$), and distilled, b. p. 71—74°; yield 36·6 g. (57%) (Found: F, 15·0. Calc. for C_2H_4BrF: F, 14·96%).

2-*Fluoroethyl Thiocyanate.*—A mixture of bromofluoroethane (50·8 g., 0·4 mol.), potassium thiocyanate (38·8 g., 0·4 mol.), ethyl alcohol (90 c.c.), and water (15 c.c.) was heated under reflux on a water-bath for 6 hours and allowed to stand overnight. After the potassium bromide had been filtered off, the alcohol and most of the water were distilled off below 83°. The residual liquid was then distilled under reduced pressure, almost the whole coming over at 78—79°/20 mm. The *thiocyanate* so obtained was further purified by redistillation; yield 32·9 g. (78·2%); b. p. 77·5—78·5°/19 mm. (Found: N, 12·9. C_3H_4NSF requires N, 13·3%).

2-*Fluoroethylsulphonyl Chloride.*—Fluoroethyl thiocyanate (the product from 0·4 mol. of bromofluoroethane) was suspended in water, cooled to 0°, and a rapid stream of chlorine passed in until a permanent green colour was obtained. The oil was then separated, extracted with ether, washed with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and then with water, and dried ($CaCl_2$). The ether was distilled off and nearly the whole of the residue came over between 81·5° and 84·5°/13 mm.; yield 35·3 g. (*i.e.*, 60·6% based on bromofluoroethane). The chlorine content of the *sulphonyl chloride* was determined by boiling with excess of dilute, halogen-free sodium hydroxide solution for 30 minutes [Found: Cl, 22·8 (Volhard), 22·6 (gravimetrically). $C_2H_4O_2SFCl$ requires Cl, 24·2%].

2-*Fluoroethyl Xanthate.*—Metallic sodium (10 g.) was dissolved in ethyl alcohol (250 c.c.), and carbon disulphide added until the solution was acid to phenolphthalein. The solution was then concentrated

until crystallisation commenced. Ether (5 vols.) was then added, and the sodium xanthate filtered off. Sodium xanthate (28·8 g., 0·2 mol.) was dissolved in ethyl alcohol (35 c.c.), bromofluoroethane (25·4 g., 0·2 mol.) added, and the solution heated under reflux for 2 hours, sodium bromide being precipitated. The mixture was then filtered and the filtrate distilled, the fraction of b. p. 200—210° being collected (18 g., 55%). The *xanthate* on redistillation gave a pale yellow liquid, b. p. 208—210°, soluble in alcohol, insoluble in water, and with an unpleasant odour (Found : F, 11·75. C_5H_9OSF requires F, 11·31%).

2-Fluoroethyl Chlorosulphonate.—FEA (32·0 g., 0·5 mol.) was added down a reflux condenser to sulphuryl chloride (37·2 g., 0·0275 mol.*), contained in a flask cooled in ice-water. Hydrogen chloride was evolved towards the end of the addition, and finally the mixture was gently heated under reflux for 45 minutes, whereupon darkening occurred. The liquid was then distilled under reduced pressure, and a fraction collected below 80°/18 mm., but chiefly in the range 76—80°/18 mm. The black residual liquid would not distil. The *fluoroethyl chlorosulphonate* was refractionated at 76—78·5°/16 mm.; yield 5·5 g. For analysis, a portion of the thrice-distilled liquid, b. p. 80°/18 mm., was used [Found : Cl, 23·0 (Stepanow); F, 12·4. $C_2H_4O_3ClFS$ requires Cl, 21·8; F, 11·7%].

2 : 2′-Difluorodiethyl Sulphate.—Sulphuryl chloride (33·8 g., 0·25 mol.) was added slowly down a reflux condenser to FEA (38·4 g., 0·6 mol.) placed in a flask cooled in ice. After the addition was complete, the mixture was gently warmed for 45 mins. during which time it darkened slightly. It was then distilled under reduced pressure and a fraction of b. p. below 70°/18 mm. (largely unchanged FEA) was collected. A second fraction came over with much fuming at about 144° and the pressure rose to 60 mm.; a solid charred residue was left. The second fraction redistilled at 144—147°/17 mm.; yield *ca.* 9 g. The compound was chlorine-free, contained fluorine, and after hydrolysis with aqueous sodium hydroxide solution, it gave a positive test for sulphate ion. For purposes of analysis the *2 : 2′-difluorodiethyl sulphate* was redistilled at 145°/18 mm. (Found : F, 20·4. $C_4H_8O_4SF_2$ requires F, 20·0%).

2-Naphthyl 2-Fluoroethyl Ether.—Fluoroethyl sulphate (5·7 g., 0·03 mol.) was added to 2-naphthol (3·6 g., 0·025 mol.) dissolved in sodium hydroxide solution (16 c.c., 10%). No reaction took place in the cold, but after 15 minutes' heating under reflux a yellow oil was produced, which solidified on cooling. The *ether* was filtered off, washed with sodium hydroxide solution and then with water, and recrystallised from aqueous ethyl alcohol, forming small colourless plates, m. p. 49·5—50° (3·5 g., 78%) (Found : F, 9·75. $C_{12}H_{11}OF$ requires F, 10·0%).

Fluoroacetaldehyde.—Manganese dioxide (69·6 g., 0·9 mol.), sulphuric acid (78·4 g., 0·8 mol.), water (45·0 g., 2·5 mols.) and FEA (64·1 g., 1·0 mol.) were mixed. After a time, the whole became warm spontaneously and liquid began to distil over. This was allowed to proceed, and finally external heat was applied to drive over as much liquid as possible up to 98°. At this stage about 50 g. of distillate had been obtained containing about 6% of aldehyde (determined gravimetrically by means of 2 : 4-dinitrophenylhydrazine). This distillate was concentrated by acidifying it with sulphuric acid, passing a stream of carbon dioxide through the boiling solution, and allowing the vapours to pass up a condenser sloping at an angle of about 45° and having water at 70—75° in its jacket. The condensate (10 g.) thus collected in a carbon dioxide–alcohol trap was again analysed and was found to have an aldehyde content of 30%.

Further concentration of the aqueous solution was carried out as follows. The liquid was distilled slowly through a nearly horizontal tube (slanting downwards away from the flask) containing fine granules of calcium chloride and a small quantity of anhydrous copper sulphate at the far end. The tube was heated in a steam jacket and the issuing vapour was condensed in a carbon dioxide–alcohol trap. Liquid distilled over betwen 92° and 98°, after which the distillate seemed to be almost entirely water. Repeated distillation of the small quantity of liquid which passed over into the trap did not give a fraction of sharp b. p., even after further drying with calcium chloride. Finally, the liquid, b. p. 89—93°, was selected for analysis (Found : F, 24·1. C_2H_3OF,H_2O requires F, 23·7%).

Gravimetric analyses of the aldehyde group by means of 2 : 4-dinitrophenylhydrazine (Iddles and Jackson, *Ind. Eng. Chem. Anal.*, 1934, **6**, 454) gave the following results, the values being calculated on the assumption that the only aldehyde present was fluoroacetaldehyde : purity of sample, 79, 82, 82·5%. In the first estimation rather less dinitrophenylhydrazine reagent was used than in the second and the third. A check analysis was carried out by the bisulphite–iodine method (Parkinson and Wagner, *ibid.*, p. 434), and this, with the same assumption, indicated a similar percentage of aldehyde. Alternatively, if the hydrate is not present as such, the fluorine content indicates that the liquid contains 78·6% of fluoroacetaldehyde, assuming that none of the impurities contains fluorine.

A more complete removal of water was then attempted. The liquid was distilled slowly over anhydrous copper sulphate, heated in a steam jacket. Distillation was continued until the temperature reached 95°. The liquid which was collected in the trap was rather viscous. It was kept over calcium chloride and was then redistilled several times until a small quantity of liquid of b. p. 57—65° was obtained. On standing, this became more and more viscous and its odour was distinct from the original aldehydic smell. Finally it set to a white solid. The action of heat on the solid gave a liquid of b. p. *ca.* 60° which went through the same changes on standing. The viscous liquid contained fluorine and slowly gave a precipitate with 2 : 4-dinitrophenylhydrazine. On warming with aqueous sodium hydroxide, the solution became reddish-brown and the characteristic resinous odour associated with aldehydes was obtained.

A sample of the *2 : 4-dinitrophenylhydrazone* of the fluoroacetaldehyde was isolated from the distillate of b. p. 89—93°. It was recrystallised from alcohol or from benzene–light petroleum (b. p. 60—80°) as small, orange-red needles. The m. p. was variable † and readings of from 141·5° to 147° were obtained for different samples (Found, for a sample of m. p. 147° : F, 7·34. $C_8H_7O_4N_4F$ requires F, 7·84%).

* These molar proportions were originally used with a view to preparing 2 : 2′-difluorodiethyl sulphate (see p. 774).

† There is a possibility of polymorphism, particularly as polymorphic forms of acetaldehyde 2 : 4-dinitrophenylhydrazone are known (Bryant, *J. Amer. Chem. Soc.*, 1933, **55**, 3201; Martin, Synge, and Bell, *Biochem. J.*, 1941, **35**, 294).

The use of potassium dichromate (in place of manganese dioxide) and sulphuric acid as oxidising agent for the fluoroethanol was attended with even less success as the aqueous distillate from the reaction mixture contained only about 1% of aldehyde.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 7th*, 1948.]

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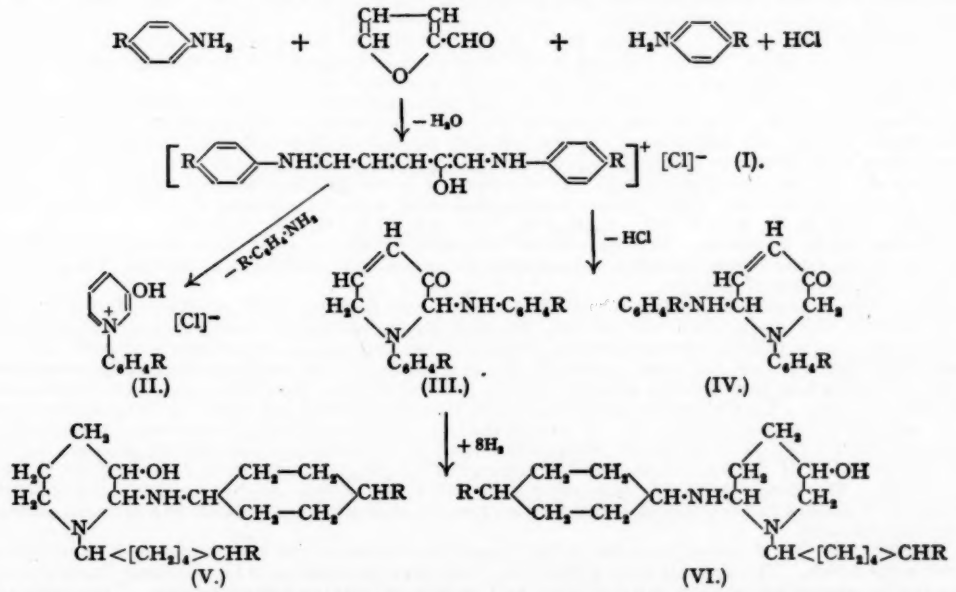
165. *The Preparation of Bases from the Coloured Compounds formed by Condensation of Furfuraldehyde with Aromatic Amines.*

By J. C. McGOWAN.

Crystalline compounds have been prepared by the action of sodium hydroxide on the coloured condensation products from aniline or *p*-toluidine with furfuraldehyde and hydrochloric acid. These compounds which are almost colourless are reconverted into the coloured compounds by mineral acids. They form monoacetates, contain a reactive methylene group, and have been catalytically reduced with the uptake of 8 mols. of hydrogen. Their reactions seem to indicate one of the formulæ (III) or (IV).

IN 1870, Stenhouse (*Annalen*, **156**, 197) found that aniline, aniline hydrochloride, and furfuraldehyde reacted together to form a deep purple compound. Since then this type of compound has been the subject of a number of investigations (Schiff, *Annalen*, 1880, **201**, 356; 1887, **239**, 349; König, *J. pr. Chem.*, 1905, **72**, 555; Dieckmann and Beck, *Ber.*, 1905, **38**, 4122; Riegel and Hathaway, *J. Amer. Chem. Soc.*, 1941, **63**, 1835; Williams and Wilson, *J.*, 1942, 506) and evidence has steadily accumulated in favour of formula (I) first suggested by Zincke and Mühlhausen (*Ber.*, 1905, **38**, 3824), who discovered that the coloured condensation compounds were converted into 3-hydroxy-*N*-phenylpyridinium salts (II) when their solutions in alcohol



or glacial acetic acid were boiled for a short time. Stenhouse (*loc. cit.*), who treated the condensation compounds from aniline and from *p*-toluidine with concentrated ammonia, obtained amorphous free bases. These bases were soluble in ether and on treatment with mineral acids re-formed the coloured crystalline salts. Zincke and Mühlhausen (*loc. cit.*) also obtained a resinous non-crystalline base from the condensation compound prepared from aniline. Details are now given for the preparation of crystalline bases from the aniline and *p*-toluidine condensation compounds. These bases are colourless and the purple compounds are regenerated when the bases are treated with mineral acids, but the full colour does not develop at once.

The reactions of the bases appear to indicate that the one derived from the aniline condensation

compound (I; R = H) is either 2- (III; R = H) or 6-*anilino*-3-*keto*-N-*phenyl*-1 : 2 : 3 : 6-*tetrahydropyridine* (IV; R = H) and the other derived from the *p*-toluidine condensation compound (I; R = CH_3) is either 2- or 6-p-*toluidino*-3-*keto*-N-p-*tolyl*-1 : 2 : 3 : 6-*tetrahydropyridine*. Only one hydrogen in the bases can be acetylated. Crystalline *monobenzoyl* and *monoacetyl* derivatives were prepared from the *p*-toluidino-compound. The aniline compound readily gave a crystalline *benzylidene* and a *furfurylidene* derivative, indicating the presence of a reactive methylene group. Under vigorous conditions of catalytic hydrogenation, 8 moles of hydrogen were taken up by both bases and the products (V or VI), isolated as *perchlorates*, were diacidic bases and had no ketonic properties. In addition, from the reduction of the *p*-toluidine compound a *product* corresponding to the uptake of 2 moles of hydrogen was isolated. This product also had no ketonic properties. Finally, the ultra-violet absorption spectra of solutions of the toluidine base and its benzoate in methyl alcohol indicate little conjugation and support the formulæ given above.

Experimental.

2(*or* 6)-*Anilino*-3-*keto*-N-*phenyl*-1 : 2 : 3 : 6-*tetrahydropyridine* (III or IV; R = H).—The coloured condensation compound of furfuraldehyde, aniline, and aniline hydrochloride (Stenhouse, *loc. cit.*) (40 g.) was shaken with 3N-sodium hydroxide (100 c.c.) and ether (300 c.c.) in a separating funnel. When all the solid had dissolved the aqueous layer was separated and the ethereal layer was washed twice with water (a little sodium chloride was added if difficulty was experienced in obtaining separation of the layers during washing). The ethereal solution was dried (Na_2SO_4), and the ether distilled off. The residue (32 g.) was allowed to stand with a little acetone until it crystallised. The crystals were filtered off, washed with ethyl alcohol, and recrystallised from this solvent. The compound thus prepared forms colourless plates, m. p. 144° (decomp.; rapid heating); yield 8 g. (Found: C, 78·2, 76·7; H, 6·0, 6·0; N, 10·0; *M*,* 273. $C_{17}H_{16}ON_2$ requires C, 77·2; H, 6·1; N, 10·6%; *M*, 264·1). The *compound* is almost insoluble in water and in sodium hydroxide solution, sparingly soluble in light petroleum, and soluble in alcohol, benzene, and acetic acid. The colourless solutions in alcohol and acetic acid become red on addition of hydrochloric acid, and the colour deepens rapidly.

Acetylation. The base (2 g.) was dissolved in dry pyridine (100 c.c.) and acetic anhydride (10 c.c.) was added. After standing for 48 hours at room temperature, the mixture was poured into water. The *acetyl* derivative separated as an oil which soon crystallised. It was filtered off, washed well with water, and purified by two recrystallisations from alcohol and one from benzene; m. p. 128° (Found: N, 9·3, 8·9. $C_{19}H_{18}O_2N_2$ requires N, 9·15%).

Attempted benzoylation. The base (4·5 g.) was dissolved in dry pyridine (150 c.c.), and benzoyl chloride (35 c.c.) added. After standing for 48 hours at room temperature the mixture was poured into water, but the oil which separated could not be made to crystallise.

Benzylidene derivative. The base (0·85 g.) and benzaldehyde (1 g.) were added to a solution of potassium hydroxide (0·8 g.) in methyl alcohol (10 c.c.). The mixture was well stirred and after 2 hours the bright yellow solid was filtered off, washed with methyl alcohol, and dried (yield 0·67 g.). This *benzylidene* derivative was sparingly soluble in ethyl alcohol, readily soluble in 1 : 4-dioxan, and was decomposed by hot glacial acetic acid. It was purified by recrystallisation first from 1 : 4-dioxan and then from ethyl alcohol; small yellow needles darkening and decomposing at 195° without melting (Found: C, 81·6; H, 5·7; N, 8·1. $C_{24}H_{20}ON_2$ requires C, 81·8; H, 5·7; N, 8·0%).

Furfurylidene derivative. This derivative, prepared as above using furfuraldehyde in place of benzaldehyde, formed orange needles from alcohol, decomposing at 160° without melting (Found: N, 8·3. $C_{22}H_{18}O_2N_2$ requires N, 8·2%).

2(*or* 6)-p-*Toluidino*-3-*keto*-N-p-*tolyl*-1 : 2 : 3 : 6-*tetrahydropyridine* (III or IV; R = CH_3).—The first part of this preparation was carried out with the condensation compound of furfuraldehyde, *p*-toluidine, and *p*-toluidine hydrochloride (Stenhouse, *loc. cit.*) (40 g.), 3N-sodium hydroxide (100 c.c.), and ether (300 c.c.), as described above for the preparation of the corresponding aniline derivative. After the ether had been distilled off from the dry ethereal extract, the residue was stirred with a small quantity of ether. Crystallisation commenced, and after the mixture had stood for 48 hours the crystalline material (12 g.) was filtered off. It was purified by several recrystallisations from either alcohol or acetone (yield 6 g.). The colourless prisms had m. p. 175° (decomp.; rapid heating) (Found: C, 77·0; H, 6·8; N, 9·75; *M*, determined as described above, 277. $C_{18}H_{20}ON_2$ requires C, 78·0; H, 6·9; N, 9·6%; *M*, 292·2). This *compound* is soluble in ether, acetic acid, hot alcohol, and hot acetone. The colourless solutions in alcohol and acetic acid develop a deep purple colour after the addition of a little concentrated hydrochloric acid.

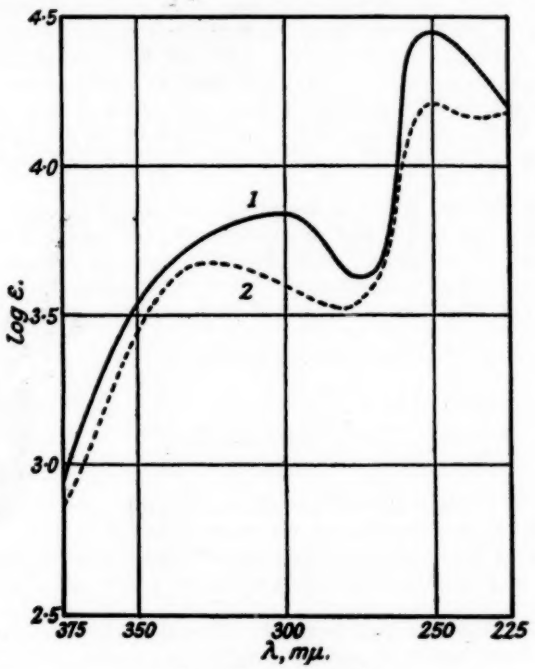
Acetylation. By the same procedure as for the anilino-analogue an oil was obtained which crystallised after some hours. The crystals were filtered off, dried over sulphuric acid in a vacuum desiccator, and purified by concentrating a solution in ether to half its bulk and leaving it to crystallise. This purification process was carried out three times. The *acetyl* derivative forms colourless prisms, m. p. 98°, very soluble in most organic solvents (Found: N, 8·2. $C_{21}H_{22}O_2N_2$ requires N, 8·4%).

Benzoylation. The base (2 g.) was dissolved in dry pyridine (100 c.c.) and benzoyl chloride (10 c.c.) was added. After standing for 48 hours at room temperature the mixture was poured into water. The crystalline material was filtered off and recrystallised several times from alcohol; rhombic prisms, m. p. 170° (Found: C, 79·3; H, 6·1; N, 7·2. $C_{26}H_{24}O_2N_2$ requires C, 78·8; H, 6·1; N, 7·1%). The ultra-violet absorption curves for this *benzoyl* derivative and for the original toluidino-compound itself are shown in the figure.

* Determined by comparing solutions in pyridine with solutions of acetanilide, using Emich's modification ("Microchemical Laboratory Manual," New York, 1932, 136) of Barger's micromethod (*Ber.*, 1904, **37**, 1754).

The acetate prepared from the aniline condensation compound and the benzoate from the toluidine compound gave solutions which remained colourless for 24 hours when small quantities were treated with equal volumes of concentrated hydrochloric acid and ethyl alcohol, although both the unsubstituted compounds when thus treated at once formed purple solutions.

Reduction of Condensation Products.—(i) 2(*or* 6)-*Anilino*-3-*keto*-N-*phenyl*-1 : 2 : 3 : 6-*tetrahydropyridine.* Reduction was carried out by dissolving 5 g. of the substance in alcohol (300 c.c.) and treating it with hydrogen at 75 atm. and 100° for 4 hours in the presence of Raney nickel (5 g.). The catalyst was filtered off, and the alcohol removed by distillation. Perchloric acid (50 c.c.; 15% wt./wt.) was added to the residue. The solid perchlorate was filtered off and dried in a vacuum over potassium hydroxide (yield 5·7 g.). The *perchlorate* of the reduced base was recrystallised twice from water and dried in a vacuum over phosphoric oxide at 100°; colourless plates (Found: C, 42·7, 43·1; H, 7·3, 7·1; N, 5·8;



Absorption spectra of:

(1) *Toluidine base.* (2) *Benzoate of toluidine base.*

Cl, 13·7, 14·8. $C_{17}H_{33}ON_2,2HClO_4$ requires C, 42·4; H, 7·1; N, 5·8; Cl, 14·7%). Attempts to acetylate and benzoylate the base failed to give crystalline products.

(ii) 2(*or* 6)-p-*Toluidino*-3-*keto*-N-p-*tolyl*-1 : 2 : 3 : 6-*tetrahydropyridine.* Reduction was effected by dissolving 13·4 g. in ethyl alcohol (250 c.c.) and treating the solution with hydrogen at 90 atm. and 100° in the presence of Raney nickel (10 g.) for 3 hours. When the catalyst and solvent were removed a gum remained. A little alcohol was added and crystals were obtained. These were filtered off and recrystallised twice from alcohol; colourless plates (0·7 g.), m. p. 133° (Found: C, 76·6; H, 8·2; N, 9·5; *M*, 268. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·2; N, 9·5%; *M*, 296·3). The formation of this *compound* has involved the uptake of 2 mols. of hydrogen.

The alcoholic mother-liquors were mixed with excess of dilute aqueous perchloric acid. The crystalline *perchlorate* that separated was recrystallised twice from water and dried in a vacuum over potassium hydroxide at 100°; yield 2·5 g. (Found: C, 44·7; H, 7·5; N, 5·4; Cl, 14·1. $C_{19}H_{34}ON_2,2HClO_4$ requires C, 44·8; H, 7·5; N, 5·5; Cl, 13·9%). An attempt to prepare a benzoate of the free base by the action of excess of sodium hydroxide solution and benzoyl chloride gave no solid product.

The reduced compounds gave no colours with mineral acids and did not react with semicarbazide, with 2 : 4-dinitrophenylhydrazine, or with salicylaldehyde in sulphuric acid.

The author's thanks are due to Mr. F. M. Page and Mr. D. Gardner for valuable assistance with this work.

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166. *Acetylene Reactions. Part I. Aminobutynes from Acetylene and Primary or Secondary Amines.*

By C. Gardner, V. Kerrigan, J. D. Rose, and B. C. L. Weedon.

The formation of 3-mono- and -di-alkylaminobut-1-ynes from amines and acetylene under pressure in the presence of a copper catalyst is described. Some by-products of this reaction are characterised, and the experimental technique of using acetylene safely in pressure reactions is outlined.

A number of different types of reaction between acetylenes and amines has been recorded. Thus, acetylene and aromatic amines have been condensed with a variety of catalysts, *e.g.*, alumina (Chichibabin, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 703), nickel (Majima, Unno, and Ono, *Ber.*, 1922, **55**, 3854), zinc chloride (I.G., B.P. 451,794), and salts of mercury, copper, or silver (Kozlov *et al.*, *J. Gen. Chem. Russia*, 1936, **6**, 250, 1089, 1341, 1897; 1937, **7**, 54, 832, 1082; Kryuk, *ibid.*, 1940, **10**, 1507). Aromatic amines have been added to monosubstituted acetylenes in the presence of boron trifluoride and mercuric oxide (Loritsch and Vogt, *J. Amer. Chem. Soc.*, 1939, **61**, 1462).

A different type of reaction between acetylene and either primary or secondary amines, resulting in the formation of mono- and di-substituted aminobutynes (I), has been described using a copper acetylide catalyst (I.G., B.P. 510,457; General Aniline and Film Co., U.S.P. 2,268,129; Reppe, Hecht, and Gassenmeier, U.S.P. 2,342,493; J. D. Rose, B.I.O.S. Final Report No. 359, Item No. 22, " Products formed from acetylene and amines," H.M.S.O. 1946).

$$RR'NH + C_2H_2 \longrightarrow (RR'N{\cdot}CH{:}CH_2)\ (II.)$$

$$RR'NH + CH_3{\cdot}CHO \longrightarrow RR'N{\cdot}CHMe{\cdot}OH\ (III.)$$

$$(II.) \text{ or } (III.) \longrightarrow RR'N{\cdot}CHMe{\cdot}C{:}CH\ (I.)$$

The publication of the German information (Rose, *loc. cit.*) of the formation of aminobutynes stimulated interest in these compounds, and their reactions were studied. They will be reported later in this series; the present communication deals largely with the formation of the aminobutynes, and confirms and amplifies the information from German sources which has already been published.

The structure of 3-diethylaminobut-1-yne (I; R = R′ = Et) was confirmed by obtaining an identical substance from acetylene and the condensation product (III) of diethylamine and acetaldehyde (B.I.O.S. Final Report No. 266, Item No. 22). That the intermediate in the formation of (I) is the vinylamine (II), and not vinylacetylene, is indicated by the fact that vinylacetylene reacts with amines, under the conditions employed, to give 2-aminobutadienes (I.G., D.R.P. 731,559).

All experiments, except those with diethylamine and aniline, were conducted in tetrahydrofuran as solvent. The secondary amines dimethylamine, diethylamine, and morpholine reacted readily to give aminobutynes in 63, 65, and 80% yields, respectively.

The reactions of the primary aliphatic amines were more complicated, and the optimum conditions for alkylaminobutyne formation were not established. The formation of higher condensation products was particularly noticeable with *iso*propylamine, though good yields of the required butynes were obtained with *n*-butyl- (65%), *cyclo*hexyl- (70%), and benzyl-amines (30%). The only identifiable product (40%) from hexamethylene diamine was 3-6′-*aminohexylaminobut*-1-*yne* (I; R = $H_2N{\cdot}[CH_2]_6{\cdot}$, R′ = H) formed by reaction of only one of the amino-groups.

Aniline only reacted satisfactorily with acetylene to give (I; R = Ph; R′ = H) under conditions that were somewhat different from those employed in the previous examples. The aniline, in alcohol solution, was partly converted into its acetate, and then treated, in the presence of a pre-formed copper acetylide on filtercel catalyst, with a nitrogen–acetylene mixture. In this manner a 41% conversion of aniline was obtained, giving a 25% yield of 3-anilinobut-1-yne.

The aminobutynes readily gave both silver and copper salts. The presence of an ethynyl group, $-C{:}CH$, was also demonstrated by a determination of active hydrogen (Zerewitinoff).

On reduction, 3-diethylaminobut-1-yne gave 2-diethylaminobutane which was identified by comparison with a specimen synthesised by an unequivocal route.

The product from a large-scale preparation of 3-diethylaminobut-1-yne contained small

amounts of higher boiling amines, $C_{11}H_{19}N$ and $C_{14}H_{28}N_2$ (*i.e.*, $2Et_2NH + 3C_2H_2$). Both these substances gave silver salts and were characterised by means of solid derivatives. The

(IV.) $CH_3{\cdot}CH(NEt_2){\cdot}CH_2{\cdot}CH(NEt_2){\cdot}C{\equiv}CH$

structures of these bases have not as yet been elucidated, but (IV) is tentatively suggested for the diamine $C_{14}H_{28}N_2$.

Experimental.

Apparatus.—Two autoclaves were employed: (*a*) an 8-l. mild steel rocking autoclave fitted with 5 vertical mild steel baffles, and (*b*) a 1·2-l. stainless steel (Baskerville and Lindsay) autoclave fitted with an electromagnetically operated stirrer. The progress of a reaction was followed by the decrease in the acetylene pressure which was not allowed to fall below *ca.* 150 lb./sq. in. Safety precautions included the installation of the acetylene cylinder outside the building, the insertion of a non-return bunsen type valve between the cylinder and the autoclave, and enclosure of the autoclave by blast-proof walls. All operations during a run were carried out by remote control.

3-*Diethylaminobut*-1-*yne* (I; R = R¹ = Et).—Diethylamine (2100 g.) and cuprous chloride (213 g.) were charged into the 8-l. autoclave, and the air displaced by flushing 3—4 times with nitrogen. The pressure in the autoclave was raised to 50 lb./sq. in. with nitrogen and then to about 200 lb./sq. in. with acetylene. Rocking and heating of the autoclave was begun, and the absorption of acetylene, initially very rapid, allowed to proceed at 80—100°. After 39 hours the rate of absorption had greatly diminished and the reaction was terminated. The product was filtered and distilled rapidly, and the distillate fractionated, giving the following (*a*) 3-diethylaminobut-1-yne (2250 g.), b. p. 123—126°, m. p. 10° (Rose, *loc. cit.*, gives b. p. 128°, m. p. 10°) (Found: N, 11·3. Calc. for $C_8H_{15}N$: N, 11·2%). The *methiodide* (deliquescent), crystallised from methanol–ether, had m. p. 108—109·5° (Found: C, 40·35; H, 6·95; N, 5·25. $C_9H_{18}NI$ requires C, 40·45; H, 6·8; N, 5·25%). The *hydrochloride*, m. p. 178—179·5°, crystallised from methanol–ether (Found: C, 59·15; H, 9·75; N, 8·25. $C_8H_{16}NCl$ requires C, 59·45; H, 9·95; N, 8·65%). (*b*) An *amine* (14 g.), b. p. 64°/25 mm., 32—34°/0·06 mm., $n_D^{14°}$ 1·4600 (Found: C, 79·5; H, 11·2; N, 8·35. $C_{11}H_{19}N$ requires C, 79·9; H, 11·55; N, 8·5%). The *methiodide*, m. p. 113—114°, formed prisms from acetone–ether (Found: N, 4·25; $C_{12}H_{22}NI$ requires N, 4·55%). (*c*) A *diamine* (*ca.* 12 g.), b. p. 56°/0·1 mm., $n_D^{21°}$ 1·4729 (after purification *via* the hydrochloride) (Found: N, 12·4. $C_{14}H_{28}N_2$ requires N, 12·5%); a Zerewitinoff determination gave 0·9 active H per molecule. The *dimethiodide*, b. p. 200—205°, crystallised in prisms from alcohol (Found: C, 37·6; H, 6·7; N, 5·25. $C_{16}H_{34}N_2I_2$ requires C, 37·8; H, 6·7; N, 5·5%). The *dihydrochloride*, m. p. 260° (decomp.), formed prisms from alcohol (Found: C, 56·5; H, 9·7; N, 9·45. $C_{14}H_{30}N_2Cl_2$ requires C, 56·5; H, 10·1; N, 9·45%). The *dipicrate*, m. p. 213° (decomp.), formed prisms from acetone (Found: C, 45·65; H, 4·8; N, 16·75. $C_{14}H_{28}N_2{\cdot}2C_6H_3O_7N_3$ requires C, 45·7; H, 5·0; N, 16·4%). On hydrogenation in methanol (Raney nickel catalyst), the diamine absorbed 2 molar proportions of hydrogen, giving a basic product, b. p. 64—65°/0·25 mm., $n_D^{21°}$ 1·4560, which was characterised as the *dimethiodide*, m. p. 193—196° (decomp.) (Found: C, 37·3; H, 7·15; N, 5·3. $C_{16}H_{38}N_2I_2$ requires C, 37·7; H, 6·9; N, 5·5%). (*d*) An amine (10 g.), b. p. 86—88°/0·09 mm., $n_D^{19°}$ 1·4785 (after purification *via* the hydrochloride) (Found: C, 77·8; H, 10·9; N, 11·3%).

2-*Diethylaminobutane.*—3-Diethylaminobut-1-yne (5 g.) in methanol (50 c.c.), was shaken, in the presence of Raney nickel, with hydrogen at 100 atm. pressure until no further absorption occurred. The product was filtered and acidified with concentrated hydrochloric acid, and the solvent evaporated. Excess of sodium hydroxide solution (20% w/v) was added to the residue, and the precipitated oil isolated by means of ether, giving 2-*diethylaminobutane* (3 g.), b. p. 130—131°/766 mm., $n_D^{20°}$ 1·4165 (Found: N, 11·05. $C_8H_{19}N$ requires N, 10·8%). The *picrate*, m. p. 116—117°, crystallised as needles from aqueous methanol (Found: N, 15·9. $C_{14}H_{22}O_7N_4$ requires N, 15·65%); its m. p. was undepressed on admixture with a specimen prepared by a method analogous to that of Leithe (*Ber.*, 1930, **63**, 800) for (+)-2-diethylaminobutane (b. p. 131°; picrate, m. p. 117°).

3-*Morpholinobut*-1-*yne* (I; $RR' = O{<}[CH_2{\cdot}CH_2]_2{>}$.—Morpholine (200 g.), tetrahydrofuran (250 c.c.), and cuprous chloride (20 g.) were treated at 85° (in the 1·2-l. autoclave) with acetylene–nitrogen, as described above, giving 3-*morpholinobut*-1-*yne* (255 g.), b. p. 76—78°/17 mm., m. p. 5·5°, $n_D^{22°}$ 1·4715 (Found: C, 69·35; H, 9·0; N, 10·35. $C_8H_{13}ON$ requires C, 69·05; H, 9·4; N, 10·05%. Zerewitinoff determination gave 1 active H per molecule). The *hydrochloride*, m. p. 157—158°, crystallised as needles from acetone (Found: N, 8·1. $C_8H_{14}ONCl$ requires N, 8·0%). The *methiodide* crystallised in prisms from alcohol, m. p. 183·5—184·5° (Found: C, 38·7; H, 5·45; N, 5·3. $C_9H_{16}ONI$ requires C, 38·45; H, 5·75; N, 5·0%).

3-*Dimethylaminobut*-1-*yne* (I; R = R′ = Me).—Dimethylamine (250 g.), tetrahydrofuran (200 c.c.), and cuprous chloride (25 g.) were treated at 85° with acetylene–nitrogen. Distillation of the product gave much recovered dimethylamine and 3-dimethylaminobut-1-yne (124 g.), b. p. 92—95° (Rose, *loc. cit.*, gives b. p. 96°). The *methiodide* formed needles from methyl alcohol, m. p. 214—216° (decomp.) (Found: C, 35·6; H, 5·9. $C_7H_{14}NI$ requires C, 35·15; H, 5·9%).

3-iso*Propylaminobut*-1-*yne* (I; R = Pr^i, R′ = H).—*iso*Propylamine (200 g.), tetrahydrofuran (200 c.c.), and cuprous chloride (20 g.) were treated at 113° with acetylene–nitrogen, giving 3-iso*propylaminobut*-1-*yne* (110 g.), b. p. 108—112°, m. p. 28—29° (Found: equiv., 111·8. $C_7H_{13}N$ requires equiv., 111·2). The *α-naphthylurea*, m. p. 111—113°, formed needles from aqueous methanol or light petroleum (b. p. 80—100°) (Found: C, 76·7; H, 7·4; N, 10·3. $C_{18}H_{20}ON_2$ requires C, 77·1, H, 7·2; N, 10·0%). The *hydrochloride*, crystallised from alcohol–ether, had m. p. 198—200° (decomp.) (Found: C, 56·6; H, 9·45. $C_7H_{14}NCl$ requires C, 56·95; H, 9·55%). The *urethane*, formed from the amine and ethyl chloroformate, was a pleasant-smelling liquid, b. p. 90—92°/13 mm., $n_D^{22°}$ 1·4420, which readily gave a silver salt with Tollens's reagent (Found: N, 7·6. $C_{10}H_{17}N$ requires N, 7·65%).

3-n-*Butylaminobut*-1-*yne* (I; R = Bu, R′ = H).—*n*-Butylamine (103 g.), tetrahydrofuran (225 c.c.),

and cuprous chloride (10 g.) were treated at 106° with acetylene–nitrogen, giving 3-*n*-butylaminobut-1-yne (115 g.), b. p. 76—79°/65 mm., $n_D^{17°}$ 1·4388 (Found: N, 11·3. Calc. for $C_8H_{15}N$: N, 11·2%) (Rose, *loc. cit.*, gives b. p. 148°). The *hydrochloride* had m. p. 122—123° (Found: C, 59·35, H, 9·6. $C_8H_{16}NCl$ requires C, 59·45, H, 9·95%). The *α-naphthylurea*, m. p. 90—91°, crystallised as needles from aqueous methanol (Found: C, 77·25; H, 7·5; N, 9·7. $C_{19}H_{22}ON_2$ requires C, 77·5; H, 7·55; N, 9·5%). The 2 : 4-*dinitrophenylurea* (cf. McVeigh and Rose, *J.*, 1945, 621) formed plates from light petroleum, m. p. 117° (Found: C, 53·6; H, 5·1; N, 17·0. $C_{15}H_{18}O_5N_4$ requires C, 53·9; H, 5·4; N, 16·8%).

3-cyclo*Hexylaminobut*-1-*yne* (I; R = C_6H_{11}, R′ = H).—*cyclo*Hexylamine (200 g.), tetrahydrofuran (200 c.c.), and cuprous chloride (20 g.) were treated at 106° with acetylene–nitrogen, giving recovered *cyclo*hexylamine (50 g.) and 3-*cyclo*hexylaminobut-1-yne (155 g.), b. p. 82—85°/17 mm., m. p. 43° (Rose, *loc. cit.*, gives b. p. 60°/5 mm., m. p. 44°). The *α-naphthylurea*, m. p. 132—133°, formed prisms from methanol (Found: C, 78·45; H, 7·7; N, 8·8. $C_{21}H_{24}ON_2$ requires C, 78·7; H, 7·5; N, 8·75%). The *hydrochloride*, m. p. 181°, crystallised in needles from ether–alcohol (Found: C, 63·6; H, 9·25; N, 7·55; Cl, 19·1. $C_{10}H_{18}NCl$ requires C, 64·0; H, 9·6; N, 7·5; Cl, 18·9%). The *picrate* formed yellow prisms from benzene, m. p. 156° (Found: C, 50·45; H, 4·8; N, 14·8. $C_{16}H_{17}N,C_6H_3O_7N_3$ requires C, 50·45; H, 5·2; N, 14·7%).

3-*Benzylaminobut*-1-*yne* (I; R = Ph·CH_2, R′ = H).—Benzylamine (200 g.), tetrahydrofuran (200 c.c.), and cuprous chloride (20 g.) were treated at 85° with acetylene–nitrogen, giving 3-benzylaminobut-1-yne (90 g.), b. p. 110—112°/20 mm., $n_D^{14°}$ 1·5290 (Rose, *loc. cit.*, gives b. p. 98°/9 mm.). The *hydrochloride*, m. p. 210—211°, crystallised as prisms from alcohol (Found: C, 67·25; H, 6·95; N, 7·15. $C_{11}H_{14}NCl$ requires C, 67·5; H, 7·2; N, 7·15%).

3-6′-*Aminohexylaminobut*-1-*yne* (I; R = NH_2·$[CH_2]_6$, R′ = H).—Hexamethylenediamine (100 g.), tetrahydrofuran (300 c.c.), and cuprous chloride (10 g.) were treated at 113—115° with acetylene–nitrogen, giving 3-6′-*aminohexylaminobut*-1-*yne* (46 g.), b. p. 118—120°/10 mm., 80—86° (mainly 83—86°)/0·6 mm., $n_D^{20°}$ 1·4700 (Found: C, 71·1; H, 11·6; N, 16·55; equiv., 86·1. $C_{10}H_{20}N_2$ requires C, 71·35; H, 12·0; N, 16·65%, equiv., 84·2).

3-*Anilinobut*-1-*yne* (I; R = Ph, R′ = H).—Hydroxylamine hydrochloride (96 g.) was added to a solution of copper sulphate pentahydrate (39·6 g.) in water (500 c.c.) and ammonia (*d* 0·88; 102 c.c.) with stirring. "Filtercel" (12 g.) was then added, and a rapid stream of acetylene passed through the mixture for 0·5 hour. The solid was filtered off, washed with water, then with alcohol, and added as an alcohol paste to the autoclave containing aniline (110 g.), alcohol (286 g.), acetic acid (43 g.), and β-dinaphthol (2·4 g.; "Cuprene" inhibitor). The stirred mixture was treated with acetylene–nitrogen for 19 hours at 20° and finally for 2 hours at 60°. After filtration, the alcohol was distilled off under reduced pressure and the resulting viscous residue treated with excess (15%) of aqueous sodium hydroxide. The product was isolated in the usual way. Distillation gave recovered aniline (65 g.) and 3-anilinobut-1-yne (18 g.), b. p. 110—120°/20 mm., which solidified readily and was recrystallised from light petroleum (b. p. 40—60°), giving colourless needles, m. p. 69—71° (U.S.P. 2,342,493 gives b. p. 110—112°/15 mm., m. p. 74°) (Found: C, 82·4; H, 7·55; N, 9·9. Calc. for $C_{10}H_{11}N$: C, 82·7; H, 7·6; N, 9·65%). The *picrate* crystallised in leaflets from aqueous methanol, m. p. 192—194° (Found: C, 51·7; H, 3·65; N, 15·25. $C_{16}H_{14}O_7N_4$ requires C, 51·35; H, 3·75; N, 15·0%).

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167. *Acetylene Reactions. Part II. Oxidation,* Hydration, and Mannich Reactions with* 3-*Aminobut*-1-*ynes.*

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Air oxidation of 3-alkyl- and -dialkyl-aminobut-1-ynes in presence of a copper catalyst gives high yields of 2 : 7-alkyl- and -dialkyl-amino-octa-3 : 5-diynes, which are catalytically hydrogenated to alkylated 2 : 7-diamino-octanes. Hydration of 3-diethylaminobut-1-yne with mercury salts gives 3-diethylaminobutan-2-one, and interaction of 3-diethylamino- and 3-morpholino-but-1-yne with formaldehyde and secondary amines affords acetylenic diamines.

RECENTLY published information from German sources on the reaction products of amines and acetylene (Rose, "Products formed by Interaction of Acetylene and Amines"; B.I.O.S. Final Report No. 359, Item No. 22, H.M.S.O. 1946; cf. Part I, preceding paper) have made the 3-mono- and -di-alkylaminobut-1-ynes readily available substances offering a fruitful field for research. This paper records some reactions which have been effected with this class of compound.

The hydration of 3-dialkylaminobut-1-ynes with mineral acids in the presence of mercury salts has been reported briefly as giving the corresponding amino-ketones (II) (I.G., B.P. 510,876), and this has been confirmed in the case of 3-diethylaminobut-1-yne (I; R = R′ = Et), 3-diethylaminobutan-2-one (II; R = R′ = Et) being obtained

Mannich-type reactions have been described with some monosubstituted acetylenes

* Patent application pending.

(Mannich and Chang, *Ber.*, 1933, **66**, 418; Jones, Marszak, and Bader, *J.*, 1947, 1578), and, in the presence of a copper catalyst with acetylene (I.G., B.P. 510,904), vinylacetylene (Coffmann, *J. Amer. Chem. Soc.*, 1935, **57**, 1978; U.S.P. 2,136,177), but-3-yn-2-ol (Rose, "Preparation of 5-Diethylaminopentan-2-ol by the Reppe Process," B.I.O.S. Final Report No. 353, Item No. 22, H.M.S.O.) and diacetylene (Microfilm of F.D 3781/45, p. 000686).

3-Diethylaminobut-1-yne (I; R = R′ = Et) reacted readily with paraformaldehyde and diethylamine or piperidine giving the acetylenic *diamines* (III; R = R′ = R″ = R‴ = Et, and R = R′ = Et, R″R‴ = C_5H_{10}) in 70 and 55% yields respectively; catalytic hydrogenation of these afforded the corresponding saturated 1 : 4-*diaminopentanes*.

The only product which could be isolated from diethylaminobutyne (I; R = R′ = Et), paraformaldehyde, and morpholine was dimorpholinomethane, but 3-morpholinobut-1-yne, with paraformaldehyde and diethylamine gave the required 4-*morpholino*-1-*diethylaminopent*-2-*yne* (III; RR′ = C_4H_8O, R″ = R‴ = Et).

RR′N·CHMe·C:CH (I.) RR′N·CHMe·COMe (II.) RR′N·CHMe·C:C·CH_2·NR″R‴ (III.)

The aerial oxidation in the presence of cuprous salts of compounds containing the ethynyl group, –C:CH, to give diacetylenes, –C:C·C:C–, has previously been studied with the acetylenic hydrocarbons (Zal'kind and Fundyler, *Ber.*, 1936, **69**, 128; *J. Gen. Chem. Russia*, 1939, **9**, 1725) and acetylenic alcohols (Zal'kind *et al.*, *ibid.*, 1937, **31**, 4283; 1939, **9**, 971, 1725; Bowden, Heilbron, Jones, and Sargent, *J.*, 1947, 1579), and that this method can be used as a highly efficient industrial process has been demonstrated by the I.G. in the oxidation of propargyl alcohol to hexa-2 : 4-diyne-1 : 6-diol (Rose, "Propargyl Alcohol; Dehydration and Oxidation to Hexadiynediol," B.I.O.S. Final Report No. 357, Item No. 22, H.M.S.O.). This reaction has now been applied to the aminobutynes (I), and it was found that oxidation was most conveniently effected by using an aqueous solution of the amine hydrochloride in the presence of only a catalytic amount of cuprous chloride. Under these conditions, a homogeneous solution was obtained, and the deposition of cuprous oxide with loss of catalyst, observed when the free

(IV.) R′RN·CHMe·C:C·C:C·CHMe·NRR′ $Et_2N·CH_2·CH{:}CH·C{:}C·C{:}C·CH{:}CH·CH_2·NEt_2$ (V.)

base is employed, was avoided. In this manner the diacetylenic *diamines* (IV; R = R′ = Et; RR′ = C_4H_8O; R = Pr^i, R′ = H; R = Bu, R′ = H) were prepared from the corresponding aminobutynes (I) in yields of 66—95%. A similar oxidation of 1-diethylaminopent-2-en-4-yne gave 1 : 10-*bisdiethylaminodeca*-2 : 8-*diene*-4 : 6-*diyne* (V) in 65% yield.

The light-absorption properties of the diacetylenic diamines (see table) are in good agreement with those of the corresponding diacetylenic glycols.

Compound.	$\lambda_{max.}$ A.	$\varepsilon_{max.}$	Compound.	$\lambda_{max.}$ A.	$\varepsilon_{max.}$
$(Et_2N·CHMe·C{:}C)_2$	2420	1,200	$(CH_3·CH[OH]·C{:}C)_2$ (1) ...	2300	1,930
	2550	720		2370	1,860
$(O<[CH_2·CH_2]_2>N·CHMe·C{:}C)_2$ †	2420 *	875	$(Me_2C·[OH]·C{:}C)_2$ (1)	2290	310
	2505 *	450		2410	300
	2570 *	365		2560	180
$(Pr^iNH·CHMe·C{:}C)_2,H_2O$	2420	630	$(HO·CH_2·CH{:}CH·C{:}C)_2$ (2)	2300	38,000
	2570	330		2370	39,000
				2470	30,000
$(Bu^iNH·CHMe·C{:}C)_2$	2470 *	1,550		2620	12,000
	2560 *	1,000		2765	20,000
				2930	30,000
$(Et_2N·CH_2·CH{:}CH·C{:}C)_2$	2290	26,000		3120	23,000
	2390	24,500			
	2490	19,000			
	2640	9,500			
	2790	15,000			
	2960	24,500			
	3150	22,000			

* Indicates an inflexion. † In methanol.

(1) Bowden, Heilbron, Jones, and Sargent (*loc. cit.*).
(2) Heilbron, Jones, and Sondheimer (*J.*, 1947, 1586).

It has been shown (Loritsch and Vogt, *J. Amer. Chem. Soc.*, 1939, **61**, 1462) that aniline reacts with monoalkylacetylenes, with a boron trifluoride–mercuric oxide catalyst, to give the

anil of the corresponding methyl alkyl ketone. Treatment of 3-diethylaminobut-1-yne (I; R = R′ = Et) with aniline under similar conditions gave diacetyl dianil (VIII).

$$\underset{\text{(VI.)}}{Et_2N{\cdot}CHMe{\cdot}C(:NPh)Me} \longrightarrow \underset{\text{(VII.)}}{Ph{\cdot}NH{\cdot}CHMe{\cdot}C(:NPh)Me} \xrightarrow{HgO} \underset{\text{(VIII.)}}{Ph{\cdot}N{:}CMe{\cdot}C(:NPh)Me}$$

The reaction probably depended on the intermediate formation of (VI) and (VII), the latter then being oxidised by mercuric oxide (the formation of mercury during the reaction was observed).

Experimental.

Analyses are by Mr. E. S. Morton. All m. p.s are uncorrected.

Light-absorption measurements were carried out in ethanol except where stated otherwise.

3-*Diethylaminobutan-2-one.*—Mercuric sulphate (0·2 g.) was added to a solution of 3-diethylaminobut-1-yne (5 g.) in sulphuric acid (*d* 1·84; 12 c.c.) and water (3 c.c.). The mixture was heated on the steam-bath for 1 hour, cooled, and poured on ice. Excess of sodium hydroxide solution (40% w/v) was added to the solution, and the precipitated oil extracted with ether. Evaporation of the ethereal solution and distillation of the residue gave 3-diethylaminobutan-2-one (4·5 g.), b. p. 56—58°/10 mm., $n_D^{17°}$ 1·4303 (Found: C, 67·0; H, 11·65; N, 9·7. Calc. for $C_8H_{17}ON$: C, 67·1; H, 11·8; N, 9·8%) (I.G., B.P. 510,876, give b. p. 168°). An aqueous alcoholic solution of the amino-ketone and semicarbazide acetate was left overnight. The *semicarbazone* was precipitated on addition of excess of alkali; it crystallised from alcohol in needles, m. p. 189·5—190·5° (Found: C, 54·25; H, 9·8; N, 27·8. $C_9H_{20}ON_4$ requires C, 54·0; H, 10·05; N, 28·0%).

1 : 4-*Bisdiethylaminopent-2-yne* (III; R = R′ = R″ = R‴ = Et).—A mixture of 3-diethylaminobut-1-yne (12·5 g.), diethylamine (8 g.), paraformaldehyde (4 g.), and dioxan (20 c.c.) was heated on the steam-bath for 13 hours, cooled, and diluted with water (400 c.c.). The product was extracted with ether, the ethereal solution evaporated, and the residue distilled, giving 1 : 4-*bisdiethylaminopent-2-yne* (15·3 g.), b. p. 104—106°/8 mm., $n_D^{18°}$ 1·4598 (Found: C, 74·4; H, 12·15. $C_{13}H_{28}N_2$ requires C, 74·2; H, 12·45%). The *dihydrochloride*, m. p. 205—206°, crystallised from alcohol–ether (Found: C, 55·25; H, 9·75; N, 9·6. $C_{13}H_{28}N_2,2HCl$ requires C, 55·1; H, 9·95; N, 9·9%). The *dipicrate*, m. p. 167—168·5°, crystallised in prisms from 2-ethoxyethyl alcohol (Found: C, 44·95; H, 4·75; N, 16·35. $C_{13}H_{28}N_2,2C_6H_3O_7N_3$ requires C, 44·9; H, 4·8; N, 16·75%). The *dimethiodide*, m. p. 168°, was prepared in acetone solution and purified from alcohol–ether (Found: C, 36·45; H, 6·65; N, 5·55. $C_{15}H_{32}N_2I_2$ requires C, 36·45; H, 6·55; N, 5·65%).

1 : 4-*Bisdiethylaminopentane.*—A solution of 1 : 4-bisdiethylaminopent-2-yne (4 g.) in methanol (50 c.c.) was shaken with hydrogen and Raney nickel until absorption was complete. After filtration, acidification, and evaporation of the solution, excess of sodium hydroxide (20%) was added to the residue, and the product isolated with ether. Distillation gave 1 : 4-*bisdiethylaminopentane* (2 g.), b. p. 105°/10 mm., $n_D^{17°}$ 1·4446 (Found: C, 73·2; H, 13·95; N, 13·2. $C_{13}H_{30}N_2$ requires C, 72·85; H, 14·1; N, 13·05%). The *dipicrate*, m. p. 192—194°, crystallised in needles from 2-ethoxyethyl alcohol (Found: C, 44·65; H, 5·4; N, 16·65. $C_{13}H_{30}N_2,2C_6H_3O_7N_3$ requires C, 44·6; H, 5·05; N, 16·9%).

1-*Piperidino-4-diethylaminopent-2-yne* (III; R = R′ = Et, R″R‴ = C_5H_{10}).—3-Diethylaminobut-1-yne (12·5 g.), piperidine (8·5 g.), paraformaldehyde (4 g.), and dioxan (20 c.c.) were heated on the steam-bath for 13 hours, and the product isolated as usual. Distillation gave 1-*piperidino-4-diethylaminopent-2-yne* (11·5 g.), b. p. 132—136°/9 mm., $n_D^{19°}$ 1·4810 (Found: C, 75·75; H, 11·5. $C_{14}H_{26}N_2$ requires C, 75·6; H, 11·8%). The *dihydrochloride*, crystallised from alcohol–ether, had m. p. 200—202° (decomp.) (Found: C, 56·55; H, 9·35; N, 9·85. $C_{14}H_{26}N_2,2HCl$ requires C, 56·95; H, 9·55; N, 9·5%). The *dipicrate*, m. p. 190—191° (decomp.), crystallised in needles from acetone (Found: C, 46·1; H, 4·6. $C_{14}H_{26}N_2,2C_6H_3O_7N_3$ requires C, 45·85; H, 4·75%). The *dimethiodide*, m. p. 198—201° (decomp.), was crystallised from alcohol–ether (Found: C, 37·6; H, 6·0; N, 5·5. $C_{16}H_{32}N_2I_2$ requires C, 37·95; H, 6·35, N, 5·55%).

1-*Piperidino-4-diethylaminopentane.*—A solution of 1-piperidino-4-diethylaminopent-2-yne (2·25 g.) in methanol was shaken with hydrogen and Raney nickel until absorption was complete. Isolation of the product gave 1-*piperidino-4-diethylaminopentane* (1·3 g.), b. p. 130—134°/12 mm., $n_D^{17°}$, 1·4644 (Found: N, 12·1. $C_{14}H_{30}N_2$ requires N, 12·35%). The *dipicrate*, m. p. 177—178°, crystallised as needles from aqueous acetone (Found: C, 45·6; H, 5·25; N, 16·5. $C_{14}H_{30}N_2,2C_6H_3O_7N_3$ requires C, 45·35; H, 5·25; N, 16·3%).

4-*Morpholino-1-diethylaminopent-2-yne* (III; RR′ = C_4H_8O, R″ = R‴ = Et).—A mixture of 3-morpholinobut-1-yne (13·9 g.), diethylamine (8 g.), paraformaldehyde (4 g.), and dioxan (20 c.c.) was heated on the steam-bath for 15 hours. Isolation of the product gave 4-*morpholino-1-diethylaminopent-2-yne* (18·5 g.), b. p. 86—90°/0·1 mm., $n_D^{23°}$ 1·4800 (Found: N, 12·45. $C_{13}H_{24}ON_2$ requires N, 12·5%). The *dipicrate*, m. p. 204—206°, formed needles from glycol monomethyl ether (Found: C, 44·3; H, 4·45; N, 16·35. $C_{13}H_{24}ON_2,2C_6H_3O_7N_3$ requires C, 44·0; H, 4·45; N, 16·45%).

2 : 7-*Bisdiethylamino-octa-3 : 5-diyne* (IV; R = R′ = Et).—A solution of 3-diethylaminobut-1-yne (75 g.) in dilute hydrochloric acid (2N; 310 c.c.) was added to a mixture of cuprous chloride (15 g.), ammonium chloride (45 g.), and water (53 c.c.). The resulting solution was warmed to 50—55° and stirred vigorously, and air was bubbled through it until green salts began to be deposited (9 hours). The mixture was cooled and filtered, and excess of concentrated ammonia solution added to the filtrate. The precipitated oil was extracted with ether, the ethereal solution evaporated, and the residue distilled, giving 2 : 7-*bisdiethylamino-octa-3 : 5-diyne* (68 g.), b. p. 130—134°/0·2 mm., $n_D^{18°}$ 1·4958 (Found: C, 77·35; H, 11·2; N, 11·25. $C_{16}H_{28}N_2$ requires C, 77·3; H, 11·35; N, 11·3%). The *dipicrate*, m. p. 230°

(decomp.) (bath preheated to 190°), crystallised as leaflets from 2-ethoxyethyl alcohol (Found : C, 47·8; H, 4·85; N, 16·3. $C_{16}H_{28}N_2,2C_6H_3O_7N_3$ requires C, 47·6; H, 4·85; N, 15·9%).

2 : 7-*Bisdiethylamino-octane*.—2 : 7-Bisdiethylamino-octa-5 : 7-diyne (4·5 g.) in methanol (50 c.c.) was hydrogenated (Raney nickel), giving 2 : 7-*bisdiethylamino-octane* (2 g.), b. p. 83—87°/0·1 mm., $n_D^{20°}$ 1·4612 (Found : N, 11·15; equiv., 128·2. $C_{16}H_{36}N_2$ requires N, 10·9%; equiv., 128·2). The *dipicrate*, m. p. 186—190° (decomp.), crystallised from 2-ethoxyethyl alcohol as leaflets (Found : C, 47·2; H, 5·6. $C_{16}H_{36}N_2,2C_6H_3O_7N_3$ requires C, 47·05; H, 5·9%).

2 : 7-*Dimorpholino-octa*-3 : 5-*diyne* (IV; RR′ = C_4H_8O).—3-Morpholinobut-1-yne (25 g.) was dissolved in hydrochloric acid (2N; 85 c.c.), and the solution added to a mixture of cuprous chloride (4 g.), ammonium chloride (12 g.), and water (14 c.c.). Aerial oxidation (for 5·5 hours) and isolation as in the case of the diethylamino-analogue gave 2 : 7-*dimorpholino-octa*-3 : 5-*dyne* (22 g.), which crystallised from alcohol in prisms, m. p. 114—115° (Found : C, 69·4; H, 8·4; N, 9·9. $C_{16}H_{24}O_2N_2$ requires C, 69·55; H, 8·75; N, 10·15%). The *dipicrate*, m. p. 224—227° (decomp.), crystallised in prisms from 2-ethoxyethyl alcohol (Found : C, 45·8; H, 4·3. $C_{16}H_{24}O_2N_2,2C_6H_3O_7N_3$ requires C, 45·75; H, 4·1%). The *dihydrochloride*, leaflets from aqueous acetone, had m. p. 242° (decomp.) (Found : N, 8·15. $C_{16}H_{24}O_2N_2,2HCl$ requires N, 8·0%).

2 : 7-*Diisopropylamino-octa*-3 : 5-*diyne* (IV; R = Pr^i; R′ = H).—A solution of 3-*iso*propylaminobut-1-yne (100 g.) in dilute hydrochloric acid (2N; 440 c.c.) was added to a mixture of cuprous chloride (20 g.), ammonium chloride (60 g.), and water (70 c.c.), and the oxidation carried out as usual. Isolation gave 2 : 7-*diisopropylamino-octa*-3 : 5-*diyne monohydrate* (105 g.), m. p. 61°, which crystallised as needles from aqueous methanol (Found : C, 70·7; H, 10·95; N, 11·95. $C_{14}H_{24}N_2,H_2O$ requires C, 70·5; H, 11·0; N, 11·75%). On standing in a desiccator this solid gives an oil, presumably the anhydrous diamine, which on exposure to the atmosphere is rapidly reconverted into the original hydrate. The *dipicrate*, m. p. 198—200° (decomp.), crystallised in prismatic needles from aqueous methanol (Found : C, 45·85; H, 4·4; N, 16·7. $C_{14}H_{24}N_2,2C_6H_3O_7N_3$ requires C, 46·05; H, 4·45; N, 16·5%). The *dihydrochloride*, purified from alcohol–ether, had m. p. 242·5—243·5° (Found : C, 56·95; H, 8·7; N, 9·25. $C_{14}H_{24}N_2,2HCl$ requires C, 57·35; H, 8·95; N, 9·55%).

2 : 7-*Diisopropylamino-octane*.—A solution of 2 : 7-diisopropylamino-octa-3 : 5-diyne monohydrate (92 g.) in methanol (800 c.c.) was hydrogenated over Raney nickel until absorption was complete. Isolation of the product gave 2 : 7-*diisopropylamino-octane* (71 g.), b. p. 92—95°/0·5 mm., $n_D^{20°}$ 1·435 (Found : N, 12·2. $C_{14}H_{32}N_2$ requires N, 12·25%). The *dihydrochloride*, crystallised from alcohol–ether, had m. p. 270° (decomp.) (Found : C, 55·65; H, 11·25. $C_{14}H_{32}N_2,2HCl$ requires C, 55·8; H, 11·35%).

2 : 7-*Di*-n-*butylamino-octa*-3 : 5-*diyne* (IV; R = Bu; R′ = H).—A solution of 3-*n*-butylaminobut-1-yne (11 g.) in dilute hydrochloric acid (2N; 45 c.c.) was added to a mixture of cuprous chloride (2 g.), ammonium chloride (6 g.), and water (7 c.c.). Aerial oxidation (14 hours) at 50° and isolation of the product gave 2 : 7-*di*-n-*butylamino-octa*-3 : 5-*diyne* (7·2 g.), b. p. 128—132°/0·06 mm., $n_D^{21°}$ 1·4952 (Found : N, 11·4. $C_{16}H_{28}N_2$ requires N, 11·3%). The *di*-α-*naphthylurea*, m. p. 163—164°, crystallised in micro-needles from aqueous alcohol (Found : C, 77·7; H, 7·1; N, 9·25. $C_{38}H_{42}O_2N_4$ requires C, 77·75; H, 7·2; N, 9·55%).

1 : 10-*Bisdiethylaminodeca*-2 : 8-*diene*-4 : 6-*diyne* (V).—A solution of 1-diethylaminopent-2-en-4-yne (4 g.; prepared from pent-2-en-4-yn-1-ol by chlorination with thionyl chloride and then treatment of the chloride with diethylamine, cf. Jones, Lacey, and Smith, *J.*, 1946, 940) in dilute hydrochloric acid (2N, 14 c.c.) was added to a mixture of cuprous chloride (0·65 g.), ammonium chloride (1·9 g.), and water (2·25 c.c.). Aerial oxidation (5·5 hours) and isolation of the product gave *bisdiethylaminodeca*-2 : 8-*diene*-4 : 6-*diyne* (2·6 g.), b. p. 155—160°/0·1 mm., $n_D^{25°}$ 1·5630 (Found : C, 78·6; H, 9·8. $C_{18}H_{28}N_2$ requires C, 79·3; H, 10·3%). The *dipicrate*, m. p. 146—148°, crystallised in prisms from aqueous acetone (Found : C, 49·0; H, 4·85; N, 15·3. $C_{18}H_{28}N_2,2C_6H_3O_7N_3$ requires C, 49·3; H, 4·7; N, 15·35%). The *dimethiodide*, needles from alcohol, had m. p. 211° (decomp.) (Found : C, 43·2; H, 6·1; N, 4·85. $C_{20}H_{34}N_2I_2$ requires C, 43·15; H, 6·15; N, 5·05%). The *dihydrochloride*, m. p. 215° (decomp.), crystallised as needles from alcohol (Found : N, 8·25. $C_{18}H_{28}N_2,2HCl$ requires N, 8·1%). Light absorption in methanol : maxima 2380, 2490, 2775, 2970, 3160; $\varepsilon_{max.}$ 28,500, 26,000, 9,500, 16,500, 27,000 and 23,000 respectively.

Diacetyl Dianil (VIII).—A mixture of aniline (45 g.), mercuric oxide (15 g.), and boron trifluoride–ether complex (6 g.) was warmed to 50°, and 3-diethylaminobut-1-yne (60 g.) added dropwise (0·5 hour) with rapid stirring. The mixture was stirred at 50° for a further 4 hours, cooled, and filtered. Distillation of the filtrate gave 3-diethylaminobut-1-yne (30 g.), aniline (15 g.), and a residue which on trituration with methanol solidified. Recrystallisation from the same solvent gave diacetyl dianil (17 g.) as yellow plates, m. p. 138° undepressed on admixture with an authentic specimen (von Pechmann, *Ber.*, 1888, **21**, 1415, gives m. p. 139°) (Found : N, 12·0. Calc. for $C_{16}H_{16}N_2$: N, 11·85%).

The authors thank Professor E. R. H. Jones for a sample of pent-2-en-4-yn-1-ol, and Dr. E. A. Braude for determining some of the absorption spectra.

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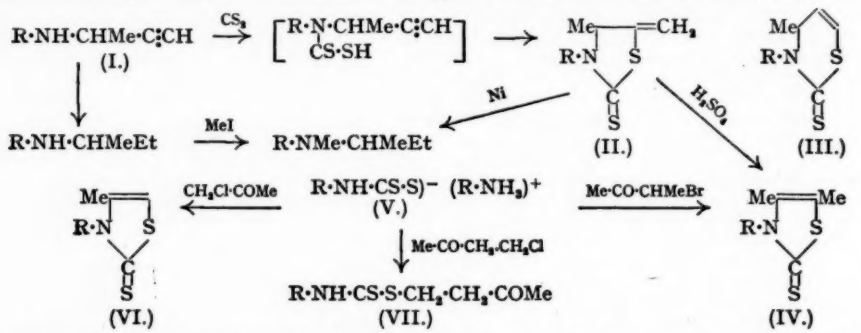
168. *Acetylene Reactions. Part III. Reaction of Aminobutynes with Carbon Disulphide.*

By J. W. Batty and B. C. L. Weedon.

Monoalkylaminobutynes (I) and carbon disulphide react readily to give 4-methyl-3-alkyl-5-methylenethiazolidine-2-thiones (II). These, on treatment with concentrated sulphuric acid, are isomerised to 4 : 5-dimethyl-3-alkylthiazol-2-thiones.

In attempting to prepare the sodium dithiocarbamate of 3-*iso*propylaminobut-1-yne (I; R = Pr^i), a neutral product was obtained in 58% yield by condensation of the amine and carbon disulphide in equimolecular proportion, the reaction being carried out in the presence of aqueous sodium hydroxide. The aminobutynes (I; R = Bu^n and *cyclo*-C_6H_{11}) gave the corresponding *n*-butyl-(87%) and *cyclo*hexyl-(70%) analogues. These reactions are thought to be similar to those which have been described between α-amino-nitriles and carbon disulphide giving mercaptothiazoles (Cook, Heilbron, and Levy, *J.*, 1947, 1598; 1948, 201), and the products from the aminobutynes have therefore been assigned the thiazolidine formulæ (II).



The alternative structure (III), which would result from an " abnormal " (anti-Markownikoff) internal addition of the intermediate dithiocarbamic acid to the triple linkage, was an obvious possibility, as such abnormal additions have been described; Kohler and Potter (*J. Amer. Chem. Soc.*, 1935, **57**, 1316) reported that phenylacetylene and thio-*p*-cresol give a β-substituted styrene derivative, and the " abnormal " addition of thiolacetic acid to acetylenes has been described by Bader, Cross, Heilbron, and Jones (this vol., p. 619).

The presence of the methylene group in (II), the thiazolidine structure of which was confirmed by other evidence given later in the paper, was established by ozonolysis to formaldehyde, and the infra-red spectrum of (II; R = Pr^i) which exhibits a fairly strong absorption band at *ca.* 875 cm.$^{-1}$ [this band is not observed in the spectra of (IV; R = Pr^i) and (VI; R = Pr^i)]. An absorption band at 870—910 cm.$^{-1}$ occurs in compounds containing the grouping $R_1R_2C{:}CH_2$ (Thompson, *J.*, 1948, 328; Barnes, Gore, Stafford, and Williams, *Anal. Chem.*, 1948, **20**, 402).

The only previously recorded example of the reaction of an acetylenic amine with carbon disulphide is that of propargylamine in alcoholic solution (Paal and Heupel, *Ber.*, 1891, **24**, 3041); the product was described as the corresponding acetylenic dithiocarbamic acid, but a consideration of its mode of formation and properties makes it virtually certain that these authors had, in fact, prepared the parent member of this series, the isomeric 5-methylenethiazolidine-2-thione. Under similar conditions, the monoalkylaminobutynes (I), referred to above, all gave products which were identical with those prepared in the presence of aqueous sodium hydroxide. Benzylaminobutyne (I; R = $Ph{\cdot}CH_2$) also gave an 81% yield of the required product, but anilinobutyne (I; R = Ph) did not react.

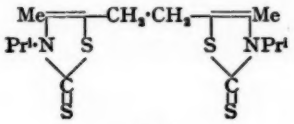
The products (II) from the monoalkylaminobutynes all exhibited ultra-violet light absorption (see Table) similar to that of 3-*methyl*- and 3-n-*butyl-thiazolidine*-2-*thione* (VIII; R = Me and Bu^n), which were synthesised by heating the appropriate β-alkylamino-ethanol with carbon disulphide (cf. the powerful chromolatory effect of the sulphur atom in the chromophore $CH{:}CH{\cdot}S{\cdot}CO{\cdot}CH_3$, Bader, Cross, Heilbron, and Jones, *loc. cit.*).

The primary condensation products (II) were readily rearranged by cold concentrated sulphuric acid, giving (80—90% yield) isomeric compounds (IV) which showed maximal light absorption at wave-lengths between 420 and 470 A. longer than those shown by the starting materials (II). The results were interpreted as indicating a migration of the double bond from

the exocyclic (II) to the cyclic (IV) position, and this conclusion was confirmed by the fact that light-absorption properties of the rearranged products were in good agreement with those of *4-methyl-3-isopropylthiazole-2-thione* (VI; R = Pr^i) which was synthesised from chloroacetone and *iso*propylammonium *iso*propyldithiocarbamate (V; R = Pr^i). The rearranged products (IV) were finally proved to be *3-alkyl-4 : 5-dimethylthiazole-2-thiones* by the synthesis of (IV; R = Pr^i and *cyclo*-C_6H_{11}) from 3-bromobutan-2-one and the appropriate dithiocarbamate (V; R = Pr^i and *cyclo*-C_6H_{11}). That these condensations did not occur by an initial dehydrobromination followed by an addition to the terminal carbon atom of methyl vinyl ketone was shown by the fact that methyl 2-chloroethyl ketone and (V; R = Pr^i) gave (84%) *3-ketobutyl N-isopropyldithiocarbamate* (VII; R = Pr^i) which was decomposed and not cyclised by treatment with cold concentrated sulphuric acid or by being heated in alcoholic solution.

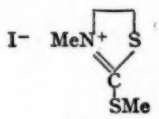
The rearrangement also occurred when (II; R = *cyclo*hexyl) was heated with either concentrated hydrochloric acid or alcoholic sodium ethoxide but not with pyridine or piperidine.

2 : 6-Di*iso*propylaminoocta-3 : 5-diyne and alcoholic carbon disulphide gave a high-melting solid which exhibited characteristic light absorption and was recovered unchanged after treatment with cold concentrated sulphuric acid. The structure (IX) is tentatively proposed for this product.



(IX.)

(VIII.)



(X.)

Treatment of the primary condensation product (II; R = *cyclo*-C_6H_{11}) with Raney nickel gave a sulphur-free base, the methiodide of which was undepressed on admixture with that of cyclo*hexylmethyl*-sec.-*butylamine*, which was synthesised from *2-cyclo*hexylaminobut-3-yne (I; R = C_6H_{11}) by hydrogenation to cyclo*hexyl*-sec.-*butylamine* followed by alkylation with methyl iodide.

	$\lambda_{max.}$ A.	$\varepsilon_{max.}$
$Me_2N{\cdot}CS{\cdot}SMe$ (1)	2760	10,000
	2460	8,000
VII; R = Pr^i	2735	9,500
	2540	9,500
	2190	8,000
(2)	2825	—
VIII; R = Me	2700	17,000
VIII; R = Bu^n	2700	17,000

	$\lambda_{max.}$ A.	$\varepsilon_{max.}$
II; R = Pr^i	2770	16,000
	ca. 3200 *	270
II; R = Bu^n	2770	17,000
	3210	2,000
II; R = *cyclo*-C_6H_{11}	2810	17,500
II; R = $Ph{\cdot}CH_2$	2800	19,000
VI; R = Pr^i	3225	12,500
	2485	2,200
IV; R = Pr^i	3240	13,500
	2360	2,700
IV; R = Bu^n	3245	13,000
	2325 *	2,600
IV; R = *cyclo*-C_6H_{11}	3230	13,000
IV; R = $Ph{\cdot}CH_2$	3240	12,000
IX	3240 †	37,000
	2750	25,500

* Inflexion. † In chloroform.

(1) Ainley, Davies, Gudgeon, Harland, and Sexton, *J.*, 1944, 147 (in *cyclo*hexane).
(2) Hamer and Rathbone, *J.*, 1943, 243.

3-Methylthiazolidine-2-thione (VIII; R = Me) reacted readily with methyl iodide giving *2-methylthiothiazoline methiodide* (X).

Experimental.

(All absorption spectra were determined in methanol solution unless otherwise stated.)

4-Methyl-3-isopropyl-5-methylenethiazolidine-2-thione (II; R = Pr^i).—(*a*) Carbon disulphide (10 c.c.) was added dropwise during 1 hour to a well-stirred mixture of sodium hydroxide (4 g.), water (30 c.c.), and 2-*iso*propylaminobut-3-yne (11·1 g.) at 50°. Stirring was continued for a further 2 hours, and the mixture was then cooled and the water-insoluble layer extracted with ether. Evaporation of the ethereal solution and distillation of the residue gave *4-methyl-3-isopropyl-5-methylenethiazolidine-2-thione* (10·8 g.) as an oil, b. p. 130—135°/0·4 mm., which solidified and was crystallised from light petroleum (b. p. 40—60°) giving colourless prisms, m. p. 43° (Found: C, 51·05; H, 6·3; N, 7·5; S, 34·0. $C_8H_{13}NS_2$ requires C, 51·3; H, 6·95; N, 7·5; S, 34·2%).

(*b*) A solution of 2-*iso*propylaminobut-3-yne (10·6 g.) and carbon disulphide (10 c.c.) in alcohol (50 c.c.) was refluxed for 4 hours, cooled, and then evaporated under reduced pressure. Distillation of the residue gave the thione (8 g.), b. p. 110—120°/0·1 mm., which solidified on standing, m. p. and mixed m. p. with specimen from (*a*) 43°.

Ozonolysis. A solution of the thione (500 mg.) in " AnalaR " acetic acid (12 c.c.) was treated with a stream of ozonised oxygen (3%) at 20° until ozone was passing freely through the solution (2 hours). Zinc dust (500 mg.) was added, and the solution distilled in steam in an atmosphere of nitrogen. The distillate was neutralised with 2N-sodium hydroxide and treated with excess of " dimedone " in 10% methyl alcohol. The mixture was boiled under reflux for 10 minutes and cooled, and the precipitate collected and weighed; yield 160 mg., m. p. 189°, undepressed by admixture with an authentic specimen of formaldehyde " dimedone."

4-*Methyl*-3-n-*butyl*-5-*methylenethiazolidine*-2-*thione* (II; R = Bu^n).—The reaction (*a*) above was repeated using 2-*n*-butylaminobut-3-yne (12·5 g.) in place of the *iso*propyl analogue, giving 4-*methyl*-3-n-*butyl*-5-*methylenethiazolidine*-2-*thione* (17·4 g.) as an oil, b. p. 140—142°/0·5 mm., $n_D^{16°}$ 1·5975 (Found: C, 53·8; H, 7·3; N, 6·8; S, 31·6. $C_9H_{15}NS_2$ requires C, 53·7; H, 7·5; N, 6·95; S, 31·85).

3-cyclo*Hexyl*-4-*methyl*-5-*methylenethiazolidine*-2-*thione* (II; R = C_6H_{11}).—(*a*) Carbon disulphide (20 c.c.) was added during 0·5 hour to 2-*cyclo*hexylaminobut-3-yne (30 g.), sodium hydroxide (8 g.), and water (60 c.c.), and the mixture stirred at 50° for 4 hours. Isolation of the water-insoluble layer gave (i) recovered aminobutyne (5 g.), and (ii) 3-cyclo*hexyl*-4-*methyl*-5-*methylenethiazolidine*-2-*thione* (26 g.) as an oil, b. p. 150—160°/0·15 mm., which solidified and was recrystallised from light petroleum (b. p. 40—60°), giving colourless prisms, m. p. 69—70° (Found: N, 6·35; S, 28·0. $C_{11}H_{19}NS_2$ requires N, 6·1; S, 27·95%).

(*b*) A solution of 2-*cyclo*hexylaminobut-3-yne (15 g.) and carbon disulphide (10 c.c.) in alcohol (30 c.c.) was refluxed for 4 hours and then evaporated under reduced pressure. Distillation of the residue gave (i) recovered aminobutyne (5·5 g.), and (ii) the thione (7 g.), b. p. 150—160°/0·15 mm., which solidified and after crystallisation from light petroleum (b. p. 40—60°) had m. p. 69°, undepressed on admixture with a specimen from (*a*).

3-*Benzyl*-4-*methyl*-5-*methylenethiazolidine*-2-*thione* (II; R = Ph·CH_2).—A solution of 2-benzylaminobut-3-yne (10 g.) and carbon disulphide (10 c.c.) in alcohol (40 c.c.) was refluxed for 6 hours and then evaporated under reduced pressure. Distillation of the residue gave 3-*benzyl*-4-*methyl*-3-*methylenethiazolidine*-2-*thione* (12 g.) as a pale yellow oil, b. p. 165—175°/0·075 mm. (Found: C, 61·45; H, 5·1; N, 6·2; S, 27·65. $C_{12}H_{13}NS_2$ requires C, 61·3; H, 5·5; N, 5·95; S, 27·25%).

1 : 2-*Di*-(4′-*methyl*-3′-iso*propyl*-2′-*thion*-5′-*thiazolyl*)*ethane* (IX).—A solution of 2 : 7-di*iso*propylamino-octa-3 : 5-diyne (5 g.) and carbon disulphide (3 c.c.) in ethanol (30 c.c.) was refluxed for 4 hours, during which time a solid was deposited. After cooling the solid was filtered off and recrystallised from pyridine, giving 1 : 2-*di*-(4′-*methyl*-3′-iso*propyl*-2′-*thion*-5′-*thiazolyl*)*ethane* (2·5 g.) as needles, m. p. 270° (decomp.) (Found: C, 51·5; H, 6·4; N, 7·6; S, 34·85. $C_{16}H_{24}N_2S_4$ requires C, 51·6; H, 6·45; N, 7·5; S, 34·4%).

4 : 5-*Dimethyl*-3-iso*propylthiazole*-2-*thione* (IV; R = Pr^i).—(*a*) 4-Methyl-3-*iso*propyl-5-methylenethiazolidine-2-thione (2·5 g.) was dissolved in cold concentrated sulphuric acid (10 c.c.) and the solution poured on crushed ice. The precipitated solid was recrystallised from aqueous methanol, giving 4 : 5-*dimethyl*-3-iso*propylthiazole*-2-*thione* (2 g.) as colourless needles, m. p. 84—86° (Found: C, 51·1; H, 6·95; N, 7·9; S, 34·25. $C_8H_{13}NS_2$ requires C, 51·3; H, 6·95; N, 7·5; S, 34·2%).

(*b*) A solution of carbon disulphide (4·85 g.) in alcohol (10 c.c.) was added slowly to a well-stirred solution of *iso*propylamine (7·5 g.) in alcohol (15 c.c.). To the resulting suspension of dithiocarbamate, 3-bromobutan-2-one (9 g., Faworsky, *J. pr. Chem.*, 1913, **88**, 657) was added slowly (0·5 hour). The solution was then refluxed for 0·5 hour, cooled, and poured into water (500 c.c.). Extraction with ether and evaporation of the ethereal solution gave a viscous oil which was dissolved in concentrated sulphuric acid (40 c.c.) with cooling in an ice-bath. The acid solution was poured on crushed ice, and the precipitated solid filtered off and recrystallised from aqueous methanol, giving the thione (7·2 g.) as colourless needles, m. p. 84—85° undepressed on admixture with a specimen from (*a*). Ozonisation of the dimethyl-*iso*propylthiazole-2-thione, as described above for the unrearranged isomer, gave no formaldehyde.

4 : 5-*Dimethyl*-3-n-*butylthiazole*-2-*thione* (IV; R = Bu^n).—A solution of 4-methyl-3-*n*-butyl-5-methylenethiazolidine-2-thione (5 g.) in concentrated sulphuric acid (15 c.c.) was poured on crushed ice. The precipitated oil slowly solidified, giving 4 : 5-*dimethyl*-3-n-*butylthiazole*-2-*thione* (4·3 g.) which crystallised from aqueous methanol or from ether as pale yellow prisms, m. p. 42—44° (Found: C, 53·7; H, 7·25; N, 6·8; S, 31·8. $C_9H_{15}NS_2$ requires C, 53·17; H, 7·15; N, 6·95; S, 31·85%).

3-cyclo*Hexyl*-4 : 5-*dimethylthiazole*-2-*thione* (IV; R = *cyclo*-C_6H_{11}).—(*a*) A solution of 3-*cyclo*hexyl-4-methyl-5-methylenethiazolidine-2-thione (2 g.) in concentrated sulphuric acid (10 c.c.) was poured on crushed ice, and the precipitated solid recrystallised from methanol, giving 3-cyclo*hexyl*-4 : 5-*dimethylthiazole*-2-*thione* (1·8 g.) as colourless needles, m. p. 104° (Found: N, 6·15; S, 28·1. $C_{11}H_{19}NS_2$ requires N, 6·1; S, 27·95%).

(*b*) A solution of carbon disulphide (4·3 g.) in alcohol (10 c.c.) was added slowly with stirring to *cyclo*hexylamine (11 g.) in alcohol (40 c.c.). To the suspension of dithiocarbamate thus obtained 3-bromobutan-2-one (8·3 g.) was added during 0·5 hour, and the resulting solution refluxed for 0·5 hour, cooled, and poured into water (500 c.c.). Isolation of the product as in the case of the 3-*iso*propyl analogue gave the thione (8 g.) which crystallised in needles from methanol, m. p. 104°, undepressed on admixture with a specimen from (*a*).

3-*Benzyl*-4 : 5-*dimethylthiazole*-2-*thione* (IV; R = Ph·CH_2).—A solution of 3-benzyl-4-methyl-5-methylenethiazolidine-2-thione (2 g.) in concentrated sulphuric acid (10 c.c.) was poured on ice. The dilute acid was decanted from the precipitated gum and the latter triturated with methanol. The resulting solid was recrystallised from the same solvent giving 3-*benzyl*-4 : 5-*dimethylthiazole*-2-*thione* (1·7 g.) as prisms, m. p. 111° (Found: C, 61·3; H, 5·5; N, 5·9; S, 27·5. $C_{12}H_{13}NS_2$ requires C, 61·3; H, 5·5; N, 5·9; S, 27·25%).

4-*Methyl*-3-iso*propylthiazole*-2-*thione* (VI; R = Pr^i).—Carbon disulphide (19·5 g.) was added slowly to a solution of *iso*propylamine (30 g.) in alcohol (100 c.c.). To the resulting dithiocarbamate suspension,

chloroacetone (23 g.) was added during 0·5 hour. After being boiled under reflux for 0·5 hour, the solution was evaporated under reduced pressure, and water (500 c.c.) added to the viscous residue. The insoluble fraction was extracted with ether. Evaporation of the ethereal solution gave **4-*methyl*-3-iso*propyl*-*thiazole*-2-*thione*** (26 g.) which crystallised in plates from aqueous methanol, or needles from light petroleum (b. p. 60—80°), m. p. 68—69° (Found : C, 48·45; H, 6·25; N, 8·45; S, 36·85. $C_7H_{11}NS_2$ requires C, 48·5; H, 6·35; N, 8·1; S, 37·0%).

3-*Ketobutyl* N-iso*Propyldithiocarbamate* (VII; R = Pr^i).—Carbon disulphide (9·7 g.) was added to a well-stirred solution of *iso*propylamine (15 g.) in alcohol (50 c.c.). To the resulting suspension, methyl 2-chloroethyl ketone (13 g.; Scheller and Zellner, U.S.P. 1,737,203) was added during 0·5 hour, and the solution was left at room temperature for 2 days and then poured into water (500 c.c.). Extraction with ether and evaporation of the ethereal solution gave **3-*ketobutyl* N-iso*propyldithiocarbamate*** (21 g.) which crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 62° (Found : C, 46·8; H, 7·05; N, 6·95; S, 31·3. $C_8H_{15}ONS_2$ requires C, 46·8; H, 7·35; N, 6·8; S, 31·25%.

cyclo***Hexyl*-sec.-*butylamine***.—A solution of 2-*cyclo*hexylaminobut-3-yne (20 g.) in methanol (75 c.c.) was shaken with hydrogen (100 atm.) and Raney nickel until absorption was complete. After filtration, the solution was acidified with concentrated hydrochloric acid and evaporated to dryness under reduced pressure. The solid hydrochloride thus obtained was treated with excess of sodium hydroxide solution (20%) and the free base isolated. Distillation gave cyclo***hexyl*-sec.-*butylamine*** (15 g.) as a colourless liquid, b. p. 86—88°/25 mm., $n_D^{16°}$ 1·4350 (Found : C, 77·2; H, 13·15; N, 9·15. $C_{10}H_{21}N$ requires C, 77·4; H, 13·5; N, 9·0%). The ***hydrochloride*** crystallised in needles from aqueous acetone, m. p. 210° (Found : C, 62·65; H, 11·2; N, 7·6. $C_{10}H_{21}N,HCl$ requires C, 62·65; H, 11·4; N, 7·3%).

cyclo***Hexylmethyl*-sec.-*butylamine***.—(*a*) Methyl iodide (9 g.) was added to a mixture of *cyclo*hexyl-*sec*-butylamine (10 g.) and powdered potassium hydroxide (5 g.). After being heated for 2 hours on the steam-bath, the mixture was cooled and treated with excess of aqueous sodium hydroxide solution (20%). The base was isolated, dissolved in dilute hydrochloric acid, and treated with a slight excess of saturated sodium nitrite solution. The precipitated oil was extracted with ether, and the tertiary base liberated from the aqueous solution by adding excess of sodium hydroxide solution. Isolation of the base gave *cyclo*hexylmethyl-*sec.*-butylamine (4·5 g.) as a colourless liquid, b. p. 90—93°/22 mm. The ***methiodide*** crystallised from alcohol–ether in needles, m. p. 174—176° (Found : C, 46·55; H, 8·2; N, 4·05. $C_{12}H_{26}NI$ requires C, 46·3; H, 8·3; N, 4·3%).

(*b*) A suspension of Raney nickel (20 c.c.) in alcohol was added to a solution of 3-*cyclo*hexyl-4-methyl-5-methylenethiazolidine-2-thione (3 g.) in alcohol (80 c.c.), and the mixture refluxed for 4 hours. The basic fraction (0·4 g.) was isolated and converted into the methiodide, which after repeated crystallisation from alcohol–ether had m. p. 170° undepressed on admixture with a specimen from (*a*).

3-*Methylthiazolidine*-2-*thione* (VIII; R = Me).—A solution of 2-methylaminoethanol (5 g.) in carbon disulphide (7 c.c.) was heated in a steel autoclave at 120—140° for 3·5 hours. After cooling, the crude product was dissolved in chloroform and the solution washed well with water, dried, and evaporated. Distillation of the residue gave an oil (5·8 g.), b. p. 90—100° (bath temp.)/10^{-4} mm., which solidified on cooling and was recrystallised from benzene–*cyclo*hexane, giving **3-*methylthiazolidine*-2-*thione*** as colourless needles, m. p. 68—69° (Found : C, 36·1; H, 5·25; N, 10·75. $C_4H_7NS_2$ requires C, 36·05; H, 5·3; N, 10·5%).

2-*Methylthiothiazoline Methiodide* (X).—3-Methylthiazolidine-2-thione (1·8 g.) was dissolved in methyl iodide (1·5 c.c.). Heat was evolved, and the mixture, which was cooled to prevent the temperature from rising above 40°, solidified. The crude product was crystallised from ethanol, giving **2-*methylthio*-*thiazoline methiodide*** (3·2 g.) as colourless leaflets, m. p. 132° (sinters at 125°) (Found : C, 22·05; H, 3·8; N, 4·85. $C_5H_9NS_2I$ requires C, 21·9; H, 3·3; N, 5·1%).

3-n-*Butylthiazolidine*-2-*thione* (VIII; R = Bu^n).—A solution of 2-*n*-butylaminoethanol (5 g.) in carbon disulphide (5 c.c.) was heated in a steel autoclave at 120—140° for 3·5 hours. After cooling, the contents of the autoclave were poured into water and the product isolated by extraction with ether. Distillation of the residue after evaporation of the ethereal solution gave **3-n-*butylthiazolidine*-2-*thione*** (4·9 g.) as a yellow oil, b. p. 90—95° (bath temp.)/10^{-4} mm., $n_D^{22·5°}$ 1·5970 (Found : C, 47·75; H, 7·35; N, 8·0. $C_7H_{13}NS_2$ requires, C, 48·0; H, 7·5; N, 8·0%).

The authors wish to thank Mr. J. D. Rose for his advice and encouragement in this work.

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169. *Acetylene Reactions. Part IV. Formation of Trimethylvinyl- and Tetramethyl-ammonium Hydroxide from Acetylene and Aqueous Trimethylamine.*

By C. GARDNER, V. KERRIGAN, J. D. ROSE, and B. C. L. WEEDON.

Interaction of aqueous trimethylamine and acetylene under pressure yields neurin (trimethylvinylammonium hydroxide) only if the reaction is carried out at or below 50°. At higher temperatures (50—100°) a mixture of neurin and tetramethylammonium hydroxide is formed, and, at temperatures above 100°, the latter is essentially the only product.

RECENT information obtained from Germany (Rose, " Products formed by interaction of acetylene and amines," B.I.O.S. Final Report No. 359, Item No. 22) indicated that aqueous

trimethylamine, when brought into reaction with acetylene under pressure, gave neurin (trimethylvinylammonium hydroxide). This appeared to be an attractive synthesis of a powerful organic base which should have many chemical and technological applications, and the reaction was studied as part of a general programme of work on the reactions of acetylene.

The apparatus used and precautions observed in this work have been described in Part I (this vol., p. 780).

The first experiment was done in the smaller (1·2-l.) autoclave (Part I, *loc. cit.*), using aqueous trimethylamine and an acetylene–nitrogen mixture at 250 ± 10 lb./sq. in., the partial pressure of the acetylene being of the order of 170 lb./sq. in. This experiment, carried out for 6·5 hours, yielded chiefly neurin, the conversion being 23%; the yield cannot be given, as the unchanged trimethylamine was not recovered.

A second experiment was carried out in the larger (8-l.) mild-steel rocking autoclave, and, owing to the relatively slower absorption of acetylene, was carried out for 30 hours by intermittent heating in four separate periods of 7·5 hours on each of four successive days. The main product from this reaction was tetramethylammonium hydroxide, identified by isolation of tetramethylammonium iodide and characterisation of this as the iododibromide (Chattaway and Hoyle, *J.*, 1923, 656).

					Composition of product:			
					NMe_4·OH.		Neurin.	
Run.	Charge.	Acetylene–N_2, (2 : 1), lb./sq. in.	Time, hrs.	Temp.	% w./v.	wt., g.	% w./v.	wt., g.
1	NMe_3 (325 g.), H_2O (600 g.).	250±20	6·5	60—65°	?	?	24 [1]	132
2	NMe_3 (890 g.), H_2O (1685 g.).	250±20	30 [2]	60—65	20	286	8	114
3	NMe_3 (156 g.), H_2O (294 g.).	250±10	17	75	12·2	57·5	11·7	55
4	NMe_3 (156 g.), H_2O (294 g.).	250±10	4·5	75	5·8	19·8	10·2	37·5
5	NMe_3 (920 g.), H_2O (1600 g.).	250±10	15	104—106	30	390 [3]	—	—
6	NMe_3 (170 g.), H_2O (300 g.).	250±10	97	30±3	1·9%	6	16·9	53

[1] Chiefly neurin, but tetramethylammonium hydroxide not determined.
[2] Intermittent heating 4 × 7·5 hrs. [3] No neurin detected.

A roughly quantitative method of analysis of mixtures of neurin and tetramethylammonium hydroxide was worked out, based on the high solubility of neurin iodide and the low solubility of tetramethylammonium iodide in water. The sample was acidified with hydriodic acid, the tetramethylammonium iodide collected, washed with alcohol, and dried, and a correction applied for the solubility of the iodide in the filtrate. The neurin content was calculated by difference from the total quaternary hydroxide (determined by titration) and the weight of tetramethylammonium iodide, calculated as hydroxide.

The results of various experiments on the interaction of trimethylamine, water, and acetylene are recorded in the table. Qualitatively, this table indicates that the formation of tetramethylammonium hydroxide is favoured by higher temperatures, and, at constant temperature (cf. runs 3 and 4), by longer reaction periods.

The spontaneous decomposition of neurin to tetramethylammonium hydroxide was demonstrated by heating a sample of neurin (17%) and tetramethylammonium hydroxide (1·9%) solution at 110—120°/5 hours. The tetramethylammonium hydroxide content increased to 6·1%. A similar sample, heated with the addition of trimethylamine showed a similar increase to 9·0% of tetramethylammonium hydroxide. In each case, a brown resin was formed which was insoluble in water and 2N-hydrochloric acid.

The mechanism of the formation of tetramethylammonium hydroxide is not clear. It is demonstrated that neurin, when boiled for 5 hours, evolves trimethylamine; the extent of this decomposition at 100° is about 10% in 5 hours, the neurin decomposed being equivalent, within the experimental error, to the trimethylamine evolved, and no tetramethylammonium hydroxide is formed. It appears, therefore, that the first stage is represented:

$$CH_2{:}CH{\cdot}NMe_3{\cdot}OH \longrightarrow NMe_3 + CH_2{\cdot}CHO(?).$$

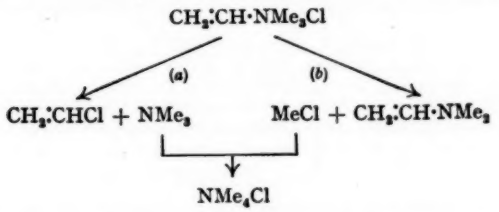
No acetaldehyde was detected, but this is not surprising, as it could not be expected to survive the strongly alkaline conditions of the reaction. When the trimethylamine is continuously removed from the reaction mixture, no tetramethylammonium hydroxide is formed; when (as

in the sealed tube experiments) the trimethylamine is retained, some " trans-methylation " mechanism must be assumed, as for example:

$$CH_2{:}CH{\cdot}NMe_3{\cdot}OH + NMe_3 \longrightarrow NMe_4{\cdot}OH + (NMe_2{\cdot}CH{:}CH_2).$$

The decomposition of neurin chloride was studied; this subject has been investigated by Meyer and Hopf (*Ber.*, 1921, **54**, 2277), who demonstrated that dimethylvinylamine was formed in very small yield. Our experiments confirm that the *isolated* yield of dimethylvinylamine is very small, but indirect evidence points to the formation of about 40% of this amine.

The decomposition of neurin chloride can proceed in two directions, (*a*) and (*b*).



By collecting the volatile constituents (trimethylamine and methyl chloride) of the decomposition products in a trap at −70°, and allowing these to recombine at room temperature, a yield of 38·5% of tetramethylammonium chloride was obtained, indicating that a decomposition had proceeded *via* route (*b*) to at least this extent. In agreement with Meyer and Hopf, we find that dimethylvinylamine is a very unstable substance, which polymerises readily and reacts violently with acidic reagents.

Experimental.

Trimethylvinylammonium Hydroxide.—Trimethylamine (325 g.) dissolved in water (600 g.) was enclosed in a stainless steel internally agitated autoclave. The air in the vessel was removed by pressing in nitrogen to 500 lb./sq. in., releasing, repressuring, and again releasing to leave a residual nitrogen pressure of 50 lb./sq. in. Acetylene was then added from a cylinder to give a total pressure of 150 lb./sq. in., and the autoclave heated to 61° during 2½ hours, by which time the total pressure had reached 250 lb./sq. in. Absorption started at 61°, and this temperature was maintained for 6·5 hours; the pressure, which fell steadily at 20 lb./sq. in./hr., was periodically restored with fresh acetylene.

The liquid product was a mixture of a dark aqueous fluid and a viscous black resin; the latter was removed with ether, and the aqueous layer shaken with active charcoal at room temperature and filtered to give a pale brown solution (550 c.c.) containing 24% wt./vol. (by titration) of trimethylvinylammonium hydroxide.

A sample (300 c.c.) of this solution was heated at 70°/15 mm. for 30 minutes to remove traces of dissolved trimethylamine, neutralised with 5N-hydrochloric acid (130 c.c.) to pH 8, evaporated at 40°/15 mm., and finally dried over phosphoric oxide in a high vacuum. Neurin chloride was obtained as white crystals (85 g.), m. p. 193—194°. The picrate formed yellow needles from water, m. p. 263—264° (decomp.) (Found: C, 42·25; H, 4·65; N, 17·6. Calc. for $C_{11}H_{14}O_7N_4$: C, 42·05; H, 4·5; N, 17·8%); Gulewitsch (*Z. physiol. Chem.*, 1898, **25**, 174) gives m. p. 264°. The iodide, formed by interaction of the chloride and potassium iodide, gave white crystals, m. p. 197°; Bode (*Annalen*, 1892, **267**, 276) gives m. p. 196°.

Trimethylethylammonium Hydroxide.—Aqueous neurin (45 c.c. of 24% wt./vol. solution) was hydrogenated over Raney nickel at ordinary temperature and 100-atm. hydrogen pressure. The resulting solution had a strong amine odour; it was filtered from catalyst and boiled. The vapours contained trimethylamine which was absorbed in water and identified as the picrate, m. p. and mixed m. p. with an authentic specimen, 216°. The residual solution contained trimethylethylammonium hydroxide (yield 50%), identified as the picrate, m. p. and mixed m. p. with an authentic specimen 299—301°.

Tetramethylammonium Hydroxide.—Trimethylamine (920 g.) and water (1600 g.) were charged into an 8-l. mild-steel autoclave, and the air was displaced by nitrogen and finally pressured to 150 lb./sq. in. with a 2 : 1 mixture of acetylene and nitrogen. The autoclave was heated and rocked at 104—106° for 15 hours, the acetylene pressure being periodically restored. The dark mixture of oil and aqueous base was extracted with ether, heated at 60°/15 mm. in a stream of nitrogen to remove trimethylamine, and clarified with carbon, yielding 1300 c.c. of 29·2% tetramethylammonium hydroxide.

A sample (100 c.c.) of the solution was neutralised with azeotropic hydriodic acid (45 c.c.) cooled to 12°, and the precipitated iodide collected, washed with alcohol, and dried. Yield 60 g. The filtrate (130 c.c.) contained 4·5 g. of iodide, as the solubility of tetramethylammonium iodide in water is 33 g./l. at 12°.

The tetramethylammonium iodide (Found: I, 63·1. Calc. for $C_4H_{12}NI$: I, 63·2%) was infusible at 330°, and was characterised by conversion into the iododibromide, m. p. 191—192° alone and in admixture with an authentic specimen prepared according to Chattaway and Hoyle (*loc. cit.*).

Analysis of Mixtures of Neurin and Tetramethylammonium Hydroxide.—The quaternary hydroxide was neutralised with azeotropic hydriodic acid cooled to 12°, the iodide filtered off, and the volume of filtrate measured. The iodide was pressed dry, washed with a little cold alcohol followed by ether, and dried to constant weight. To this weight is added a factor of 33 g./l. of filtrate as a correction for the

solubility of the iodide in water at 12°; Walden (*Z. physikal. Chem.*, 1906, **55**, 708) gives 20·1 g./l. at 0°, 53·1 g./l. at 25°. The total hydroxide-ion content was determined by titration, and neurin calculated by difference.

In blank experiments with pure tetramethylammonium hydroxide, and mixtures of this with neurin, recovery of added tetramethylammonium hydroxide varied from 96 to 104%.

Formation of Tetramethylammonium Hydroxide from Neurin.—Neurin solution (20·5 c.c. of 17% w/v, containing 1·9% of tetramethylammonium hydroxide) was heated in a sealed tube at 110—120° for 5 hours. The contents of the tube, a mixture of a clear aqueous fluid and a brown resin, were extracted with ether, and the aqueous layer analysed as above. The tetramethylammonium hydroxide content was 6·1% w/v.

A similar experiment, in which 1·65 g. of trimethylamine were dissolved in the neurin–tetramethylammonium hydroxide solution, showed an increase in the tetramethylammonium hydroxide content to 9%.

Decomposition of Neurin.—A solution of neurin (50 c.c. of 17% w/v) containing 1·9% w/v of tetramethylammonium hydroxide was boiled gently under reflux in a stream of nitrogen, the vapours from the reflux condenser being led through two traps in series containing standard sulphuric acid. After 5 hours, the flask was allowed to cool for 30 minutes, the stream of nitrogen being continued. The residual neurin, and the trimethylamine absorbed in the sulphuric acid traps, were then determined by titration. The decrease of neurin content corresponded to a loss of 0·0092 g.-mol., whilst the trimethylamine evolved was 0·0106 g.-mol. There was no detectable increase in the tetramethylammonium hydroxide content.

In a control experiment with pure tetramethylammonium hydroxide solution, no trimethylamine was evolved in 5 hours.

Decomposition of Neurin Chloride.—Neurin chloride (75 g.) was distilled with a free flame in a current of nitrogen, the decomposition products being collected in a trap cooled with acetone–solid carbon dioxide. Distillation was continued until the vapour temperature was 95°. The total distillate (55 c.c.) was redistilled in nitrogen through a 3-in. column packed with Monel metal gauze spirals, giving 50 c.c. of a liquid, b. p. <15°; 1 g. of liquid, b. p. 31—33°, was collected which decolourised alkaline permanganate, reacted violently with 2 : 4-dinitrophenylhydrazine sulphate, and polymerised rapidly. The low-boiling fraction (50 c.c.; 40 g.) was sealed in a tube and set aside at room temperature. After 24 hours a white crystalline precipitate, m. p. >300° (26 g.), of tetramethylammonium chloride was formed, identified as the picrate, m. p. and mixed m. p. with an authentic specimen 314° (decomp.) (Lossen, *Annalen*, 1876, **181**, 374, gives m. p. 312—313°).

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170. *Acetylene Reactions. Part V. Reactions of Phenylacetylene with Secondary Amines.*

By J. D. ROSE and R. A. GALE.

Interaction of phenylacetylene and morpholine in the presence of cuprous chloride gives 3-*morpholino*-1 : 4-*diphenylbut*-1-*yne* (VI) and a second isomeric *base*, probably 1-morpholino-1 : 4-diphenylbut-3-yne (III). The structure of (VI) is confirmed by unambiguous synthesis, and the structure of (III) is made probable by the synthesis of the other two of the four possible isomers, with neither of which (III) is identical.

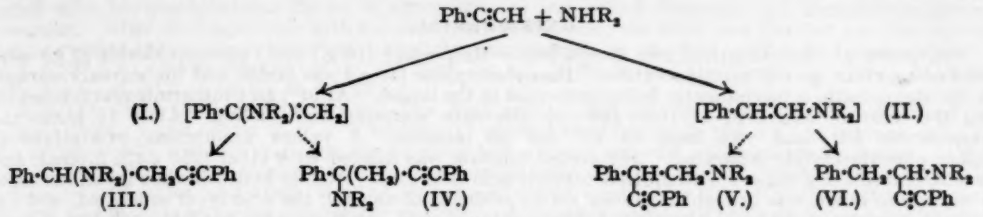
THE investigation of the reactions of phenylacetylene was initiated to determine to what extent this substance could be used as a laboratory model for the reactions of acetylene itself. In work on the use of acetylene under pressure in organic synthesis, the sensitivity of such reactions to the surface conditions of the pressure vessel used greatly impeded the progress of the investigations. No reaction could be abandoned with confidence as a failure until three successive fruitless attempts had been made; reactions which failed on the first attempt frequently proceeded, if badly, on the second, and gave good results in the third and successive experiments. Since each experiment requires a considerable time it was thought that much effort might be saved if phenylacetylene could be used as a laboratory model for preliminary investigations to indicate what reactions would be most likely to succeed using acetylene itself.

It was first necessary to establish some parallelism between the reactions of acetylene and those of phenylacetylene, and the formation of 3-alkyl- or 3-dialkyl-aminobut-1-ynes from acetylene and amines (cf. Part I, this vol., p. 780) was chosen as a comparison case.

The interaction of acetylene and a primary or secondary amine is considered to proceed *via* the formation of an unstable and reactive intermediate vinylamine, which adds a further molecule of acetylene giving the aminobutyne, thus:

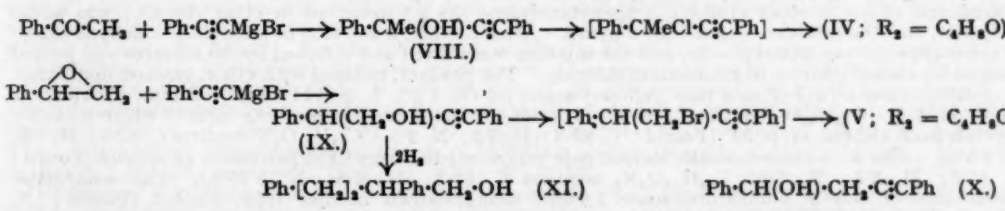
$$CH{:}CH + NHR_2 \longrightarrow [CH_2{:}CH{\cdot}NR_2] \xrightarrow{C_2H_2} CH{:}C{\cdot}CH(CH_3){\cdot}NR_2$$

If analogous reactions occur with phenylacetylene, there are two possibilities, (I) and (II), for the intermediate vinylamine, and four, (III), (IV), (V), and (VI), for the final product.



Morpholine (1 mol.) and phenylacetylene (2 mols.) reacted vigorously in the presence of a cuprous chloride catalyst, giving a mixture of basic products from which two isomeric bases, $C_{20}H_{21}ON$, m. p.s 70° and 88°, could be separated by fractional crystallisation from alcohol.

The base, m. p. 70°, was identified as 3-*morpholino*-1 : 4-*diphenylbut*-1-*yne* (VI; $R_2 = C_4H_8O$) by unambiguous synthesis. Phenylacetaldehyde was caused to react with phenylacetylenylmagnesium bromide, and the resulting 1 : 4-*diphenylbut*-1-*yne*-2-*ol* (VII) was converted *via* the bromide into (VI; $R_2 = C_4H_8O$), identical with the product obtained directly from phenylacetylene and morpholine. Identification of the base, m. p. 88°, isolated in much lower yield than its isomeride, proved more difficult; although its structure cannot be regarded as definitely established, it is probably 1-*morpholino*-1 : 4-*diphenylbut*-3-*yne* (III; $R_2 = C_4H_8O$), since the remaining two isomerides (IV and V; $R_2 = C_4H_8O$) have been synthesised and are different from this base. 1 : 3-Diphenylbut-1-yn-3-ol (VIII) was prepared from acetophenone and phenylacetylenylmagnesium bromide, giving a product identical with that obtained by Nef (*Annalen*, 1899, **308**, 264) by long interaction of sodium phenylacetylide and acetophenone in ether. This was converted *via* its chloride into 3-*morpholino*-1 : 3-*diphenylbut*-3-*yne*, which had m. p. 99° and depressed the m. p. of the base, m. p. 88°, to 65—75°. The remaining isomeride was prepared as follows. Phenylacetylenylmagnesium bromide reacted vigorously with styrene oxide to give, in good yield, 1 : 3-*diphenylbut*-1-*yn*-4-*ol* (IX). This structure and mode of addition of the Grignard to the epoxide was made probable by the work of Kharasch and Clapp (*J. Org. Chem.*, 1938, **3**, 355) who established that addition of styrene oxide to phenylmagnesium bromide gives 2 : 2-diphenylethyl alcohol, whereas reversal of this order by addition of the Grignard solution to the styrene oxide gives the isomeric 1 : 2-diphenylethyl alcohol. There was, therefore, a probability that addition of styrene oxide to phenylacetylenylmagnesium bromide would give 1 : 3-diphenylbut-1-yn-4-ol (IX), and not the isomeric 1 : 4-diphenylbut-1-yn-4-ol (X). This was confirmed by hydrogenation of the product to 2 : 4-*diphenylbutanol* (XI), a liquid which could not be induced to crystallise and was different from the 1 : 4-diphenylbutanol described by Stoermer and Schenk (*Ber.*, 1928, **61**, 2320).


Ph·CH₂·CHO + Ph·C:CMgBr → Ph·CH₂·CH(OH)·C:CPh → [Ph·CH₂·CHBr·C:CPh] → (VI; R₂ = C₄H₈O)
(VII.)
Ph·CO·CH₃ + Ph·C:CMgBr → Ph·CMe(OH)·C:CPh → [Ph·CMeCl·C:CPh] → (IV; R₂ = C₄H₈O)
(VIII.)
Ph·CH—CH₂ + Ph·C:CMgBr →
O
Ph·CH(CH₂·OH)·C:CPh → [Ph·CH(CH₂Br)·C:CPh] → (V; R₂ = C₄H₈O)
(IX.)
+2H₂
Ph·[CH₂]₂·CHPh·CH₂·OH (XI.)
Ph·CH(OH)·CH₂·C:CPh (X.)

The acetylenic alcohol (IX) was converted *via* its bromide, in very low yield, into 4-*morpholino*-1 : 3-*diphenylbut*-1-*yne*, which had m. p. 126° and was different from the base, m. p. 88°. By elimination, therefore, it is considered probable that the structure of the base, m. p. 88°, is (III; $R_2 = C_4H_8O$), and this implies, in turn, that the primary condensation of phenylacetylene and morpholine does, in fact, proceed in both possible ways, giving (I) and (II).

At attempt to hydrogenate the base, m. p. 88°, in the hope of synthesising the hydrogenated product for comparison was unsuccessful; hydrogenation with Raney nickel and hydrogen at ordinary temperature and pressure disrupted the molecule completely.

The behaviour of piperidine was parallel with that of morpholine, but the only product isolated was 3-*piperidino*-1 : 4-*diphenylbut*-1-*yne* (VI; $R_2 = C_5H_{10}$), which was identified by

comparison of its *picrate* and *methiodide* with the same derivatives formed from the product obtained by interaction of 3-bromo-1 : 4-diphenylbut-1-yne and piperidine.

Experimental.

Interaction of Phenylacetylene and Morpholine.—Morpholine (16 g.) and cuprous chloride (2 g.) were warmed together, giving partial solution. Phenylacetylene (40 g.) was added and the mixture warmed on the steam-bath, a thermometer being immersed in the liquid. At 98°, an exothermic reaction set in, and the mixture was kept at 100—105° by alternate warming and cooling. After 1½ hours the temperature fell, and was kept at 97° for 30 minutes. A yellow amorphous precipitate of copper phenylacetylide separated. The cooled mixture was diluted with ether (250 c.c.), filtered, and the ethereal solution shaken with 2N-hydrochloric acid (100 c.c.). An oily hydrochloride layer, insoluble in water and ether, was brought into solution by addition of alcohol, the acid layer separated, and the extraction repeated (50 c.c. of 2N-HCl). The combined acid solutions were basified with 10N-sodium hydroxide, and the precipitated oil collected in ether, dried, and distilled, giving a pale yellow viscous oil (21·5 g.), b. p. 154—160°/0·06 mm. This was dissolved in hot alcohol (40 c.c.), cooled, and scratched; a crystalline mass then separated. The crystals were collected, washed with ice-cold alcohol (5 c.c.), and dried. Yield 10·15 g., m. p. 56—60°. Recrystallisation from alcohol (20 c.c.) gave 6·6 g., m. p. 68—70°, which after a further crystallisation from alcohol gave 3-*morpholino*-1 : 4-*diphenylbut*-1-*yne* as colourless prisms, m. p. 70° (Found : C, 82·3; H, 7·2; N, 4·8. $C_{20}H_{21}ON$ requires C, 82·4; H, 7·2; N, 4·8%). The *picrolonate* formed yellow prisms from butyl alcohol, m. p. 220° (Found : C, 65·0; H, 5·25; N, 12·7. $C_{20}H_{21}ON,C_{10}H_8O_5N_4$ requires C, 64·9; H, 5·2; N, 12·6%). The *picrate* had m. p. 151° (Found : C, 59·65; H, 4·55; N, 11·0. $C_{10}H_{21}ON,C_6H_3O_7N_3$ requires C, 60·0; H, 4·6; N, 10·7%). The *perchlorate* formed white prisms from alcohol, m. p. 191° (Found : N, 3·4. $C_{20}H_{21}ON,HClO_4$ requires N, 3·5%). The *methiodide* formed white prisms from ether–alcohol, m. p. 186° (decomp.) (Found : C, 58·2; H, 5·6; N, 3·4. $C_{21}H_{24}ONI$ requires C, 58·2; H, 5·55; N, 3·25%). The mother liquors from crystallisation of this base were concentrated, and the residue fractionally crystallised. A little more of the above base, m. p. 70°, was obtained as the least soluble fraction, and a second *base* (2·9 g.), m. p. 88°, was obtained as white crystals from alcohol (Found : C, 82·4; H, 7·5; N, 4·7. $C_{20}H_{21}ON$ requires C, 82·4; H, 7·2; N, 4·8%). The *picrate* separated from alcohol in yellow plates, m. p. 144° (Found : C, 59·65; H, 4·45; N, 10·5. $C_{20}H_{21}ON,C_6H_3O_7N_3$ requires C, 60·0; H, 4·6; N, 10·7%). The *picrolonate* formed pale yellow prisms from alcohol, m. p. 163° (decomp.) (Found : C, 64·85; H, 5·15; N, 12·75. $C_{20}H_{21}ON,C_{10}H_8O_5N_4$ requires C, 64·9; H, 5·2; N, 12·6%).

The ethereal solution from which the basic products had been isolated was dried and distilled; some phenylacetylene was recovered, and a little acetophenone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic specimen 249°) distilled at 10 mm. High-vacuum distillation gave (i) a yellow oil, b. p. 140—146°/0·2 mm. (2·15 g.), which solidified on cooling, and (ii) a yellow solid, b. p. 164—165°/0·2 mm. On crystallisation from alcohol, fraction (i) gave a *substance* as white needles, m. p. 74° (Found : C, 90·05; H, 5·9. $C_{32}H_{26}O$ requires C, 90·1; H, 6·1). Fraction (ii) gave a *ketone*, m. p. 89° (Found : C, 85·9; H, 6·6. $C_{16}H_{14}O$ requires C, 86·4; H, 6·3%). The 2 : 4-*dinitrophenylhydrazone* formed orange-yellow needles from alcohol, m. p. 190° (Found : C, 66·2; H, 4·25; N, 14·2. $C_{22}H_{18}O_4N_4$ requires C, 65·7; H, 4·5; N, 13·9%).

2-*Morpholino*-1 : 4-*diphenylbutane.*—3-Morpholino-1 : 4-diphenylbut-1-yne (2·92 g.) was dissolved in methyl alcohol (50 c.c.) and hydrogenated at ordinary temperature and pressure, using Raney nickel catalyst. Absorption (450 c.c.; calc. for $2H_2$: 448 c.c.) was complete in 20 minutes. The filtered solution was distilled, giving the *base* as a colourless viscous oil, b. p. 152°/0·1 mm. (Found : C, 81·35; H, 8·2; N, 5·0. $C_{20}H_{25}ON$ requires C, 81·35; H, 8·45; N, 4·75%). The *hydrochloride* separated from acetone in white needles, m. p. 158° (Found : N, 4·6; Cl, 11·2. $C_{20}H_{25}ON,HCl$ requires N, 4·2; Cl, 10·7%). The *picrolonate* formed yellow needles from alcohol, m. p. 198° (Found : C, 64·9; H, 5·6; N, 12·5. $C_{20}H_{25}ON,C_{10}H_8O_5N_4$ requires C, 64·9; H, 5·6; N, 12·5%).

1 : 4-*Diphenylbut*-1-*yn*-3-*ol.*—To a Grignard solution prepared from ethyl bromide (25·3 g.) and magnesium (7 g.) in ether (100 c.c.), phenylacetylene (38 g.) dissolved in ether (90 c.c.) was added dropwise, and the mixture refluxed for 2 hours. After cooling, a solution of phenylacetaldehyde (32 g.) in ether (90 c.c.) was added slowly, and the mixture was stirred and refluxed for 30 minutes and poured into an ice-cooled solution of ammonium chloride. The product, isolated with ether, gave on distillation 1 : 4-*diphenylbut*-1-*yn*-3-*ol* as a pale yellow viscous oil (31·5 g.), b. p. 144—145°/0·2 mm. (Found : C, 86·3; H, 6·1. $C_{16}H_{14}O$ requires C, 86·5; H, 6·3%). The *α-naphthylurethane* formed white wax-like crystals from alcohol, m. p. 94° (Found : C, 82·3; H, 5·3; N, 3·5. $C_{27}H_{21}O_2N$ requires C, 82·8; H, 5·3; N, 3·6%). The 3 : 5-*dinitrobenzoate* formed pale yellow needles from light petroleum or alcohol (Found : C, 66·3; H, 3·8; N, 6·9. $C_{23}H_{16}O_6N_2$ requires C, 66·3; H, 3·8; N, 6·75%). The *α-naphthylamine* salt of the 3 : 5-dinitrobenzoate formed orange-brown needles from alcohol (Found : N, 7·6. $C_{23}H_{16}O_6N_2,C_{10}H_7NH_2$ requires N, 7·4%).

The alcohol above (20 g.) was dissolved in benzene (120 c.c.), and phosphorus tribromide (20 c.c.) added dropwise with stirring. The solution became dark, but at the end of the addition had turned pale green; it was heated on the steam-bath for 30 minutes, poured on ice, collected in ether, and distilled, giving the crude bromide (21·2 g.), b. p. 160—170°/0·4 mm. This bromide (5 g.) was heated with morpholine (3·5 g.) at 100—110° for 30 minutes, cooled, diluted with dry ether, and filtered from morpholine hydrobromide. From the ethereal solution, basic material was isolated by 2N-acid, and the base was regenerated, extracted with ether and distilled. The yellow oil, b. p. 150—155°/0·02 mm., crystallised on cooling, and after recrystallisation from alcohol had m. p. 70°, undepressed by admixture with 3-morpholino-1 : 4-diphenylbutyne prepared directly from phenylacetylene and morpholine. Identity was further established by the picrate, m. p. and mixed m. p. 151°, and the perchlorate, m. p. and mixed m. p. 191°.

1 : 3-*Diphenylbut*-1-*yn*-3-*ol.*—This alcohol has been prepared by Nef (*loc. cit.*) by interaction of

sodium phenylacetylide and acetophenone in ether. The following procedure is preferable. To a Grignard solution prepared from magnesium (4·7 g.), ethyl bromide (17·5 g.), and ether (90 c.c.), phenylacetylene (25 g.) was added slowly and the mixture refluxed with stirring for 2 hours. To the cooled solution, acetophenone (20 g.) in ether (60 c.c.) was added dropwise, and the mixture stirred overnight. After decomposition with ice and hydrochloric acid, the ether was distilled and the reddish viscous residue (40 g.) was crystallised from light petroleum (b. p. 40—60°), giving 1 : 3-diphenylbut-1-yn-3-ol (25 g.) as white needles, m. p. 75° (Nef, *loc. cit.*, gives m. p. 77°) (Found : C, 86·3; H, 6·35. Calc. for $C_{16}H_{14}O$: C, 86·5; H, 6·3%).

3-*Morpholino*-1 : 3-*diphenylbut*-1-*yne*.—The diphenylbutynol (above; 18·5 g.) was dissolved in benzene (50 c.c.) and cooled to 0°. A solution of phosphorus trichloride (2·4 c.c.) in benzene (20 c.c.) was added slowly with shaking, and the mixture left without external cooling for 45 minutes. After dilution with ether, the solution was washed successively with water, saturated sodium hydrogen carbonate, and water, and dried ($MgSO_4$), and the ether removed below 30°. The product was a dark viscous oil (20 g.) which was not further purified. A mixture of this chloride (3 g.) and morpholine (3 g.) was kept at ordinary temperature for 4 days. Crystals of morpholine hydrochloride separated. The mixture was diluted with ether and filtered, and the basic product isolated by extraction with 2N-hydrochloric acid, regeneration with sodium hydroxide, and extraction with ether. After distillation of the ether the residue, a dark viscous oil, was heated at 100°/20 mm. for 1 hour, and dissolved in alcohol (1 c.c.). White crystals separated which after recrystallisation from alcohol gave 3-*morpholino*-1 : 3-*diphenylbut*-1-*yne* as white needles, m. p. 99° (Found : C, 82·35; H, 7·1; N, 4·75. $C_{20}H_{21}ON$ requires C, 82·4; H, 7·2; N, 4·8%). The *picrate* formed yellow needles from alcohol, m. p. 156° (decomp.) (Found : C, 59·6; H, 4·6; N, 11·2. $C_{20}H_{21}ON,C_6H_3O_7N_3$ requires C, 60·0; H, 4·6; N, 10·7%).

1 : 3-*Diphenylbut*-1-*yn*-4-*ol*.—To a Grignard solution prepared from ethyl bromide (18 g.), magnesium (4 g.), and a crystal of iodine, in anhydrous ether (30 c.c.), was added dropwise during 30 minutes a solution of phenylacetylene (17 g.) in ether (30 c.c.). The mixture was boiled under reflux for 30 minutes with stirring, and a solution of styrene oxide (20 g.) in ether (30 c.c.) was then added during 30 minutes. The mixture was stirred under reflux for 1 hour, cooled, and cautiously decomposed with ice and dilute sulphuric acid. Distillation of the ethereal layer afforded 1 : 3-*diphenylbut*-1-*yn*-4-*ol* as a colourless viscous oil, b. p. 145—150°/0·2—0·25 mm., $n_D^{20°}$ 1·6085 (Found : C, 86·55; H, 6·25. $C_{16}H_{14}O$ requires C, 86·5; H, 6·3%). The *phenylurethane* formed prisms from alcohol, m. p. 99—100° (Found : C, 81·25; H, 5·75; N, 4·5. $C_{23}H_{19}O_2N$ requires C, 80·95; H, 5·6; N, 4·1%). The 3 : 5-*dinitrobenzoate* formed pale yellow needles from benzene, m. p. 142° (Found : C, 66·5; H, 3·8; N, 6·7. $C_{23}H_{16}O_6N_2$ requires C, 66·3; H, 3·8; N, 6·7%).

2 : 4-*Diphenylbutanol*.—The diphenylbutynol (above, 10 g.) dissolved in methyl alcohol (50 c.c.) was hydrogenated at ordinary temperature and pressure over Raney nickel catalyst. Absorption (1990 c.c. at N.T.P. Calc., 2010 c.c.) was complete in 75 minutes. The product, isolated by distillation in 90% yield, had b. p. 120°/0·03 mm., $n_D^{17°}$ 1·5717 (Found : C, 84·7; H, 7·6. $C_{16}H_{18}O$ requires C, 84·9; H, 7·9%). The 3 : 5-*dinitrobenzoate* formed needles from alcohol, m. p. 96° (Found : C, 65·9; H, 4·9; N, 6·9. $C_{23}H_{20}O_6N_2$ requires C, 65·7; H, 4·8; N, 6·7%).

4-*Morpholino*-1 : 3-*diphenylbut*-1-*yne*.—1 : 3-Diphenylbut-1-yn-4-ol (10 g.) was treated with phosphorus tribromide (4 c.c.). After the initial exothermic reaction had subsided the mixture was heated on the steam-bath for 1 hour, diluted with ether, washed successively with water, sodium hydrogen carbonate, and water, dried, and evaporated. To the cold residue morpholine (5 c.c.) was added, and the mixture set aside for 3 days. Morpholine hydrobromide was collected after dilution with ether, and the basic material isolated. Evaporation of the ether solution of the basic portion left a very small amount of a brown oil which slowly crystallised and was recrystallised from alcohol, giving white needles of 4-*morpholino*-1 : 3-*diphenylbut*-1-*yne*, m. p. 126° (Found : N, 4·8. $C_{20}H_{21}ON$ requires N, 4·8%).

1-*Morpholino*-2 : 4-*diphenylbutane*.—2 : 4-Diphenylbutanol (12·7 g.) was brought into reaction with phosphorus tribromide (10 g.). When the initially vigorous reaction had subsided the mixture was heated on the steam-bath for 1 hour, cooled, poured into water, and extracted with ether. The ethereal solution, after successive washing with water, saturated aqueous sodium hydrogen carbonate, and water, was dried and evaporated, giving a colourless oil (12·1 g.). Morpholine (8 c.c.) was added, and the mixture set aside for 5 days. Morpholine hydrobromide was filtered from the ethereal solution, and the base extracted with hydrochloric acid and regenerated. The base distilled at 150°/0·05 mm. as a pale yellow viscous oil (Found : C, 81·5; H, 8·7; N, 5·0. $C_{20}H_{25}ON$ requires C, 81·4; H, 8·5; N, 4·8%). The *hydrochloride* separated from alcohol with a molecule of alcohol of crystallisation, m. p. 236—237° (decomp.) (Found : C, 69·8; H, 7·9; N, 3·7. $C_{20}H_{25}ON,HCl,C_2H_6O$ requires C, 69·9; H, 8·4; N, 3·7%). The *picrate* formed yellow plates, m. p. 145° from alcohol (Found : C, 59·2; H, 5·35; N, 10·9. $C_{20}H_{25}ON,C_6H_3O_7N_3$ requires C, 59·5; H, 5·35; N, 10·7%).

Reaction of Phenylacetylene and Piperidine.—Piperidine (4 g.) was warmed with cuprous chloride (0·5 g.), and phenylacetylene (10 g.) added. The exothermic reaction which began on heating was controlled at 98—102°, and the mixture finally heated on the steam-bath for 2 hours. The product, diluted with ether and filtered, was separated into basic and neutral portions. The latter on distillation gave a little acetophenone and diphenyldiacetylene, m. p. and mixed m. p. with an authentic specimen, 88°. The basic portion was distilled giving a yellow oil, b. p. 156—160°/0·15 mm. This was treated with picric acid (2·5 g.) in alcohol (200 c.c.), and the product crystallised to constant m. p. 3-*Piperidine*-1 : 4-*diphenylbut*-1-*yne picrate* separated from alcohol as yellow needles (3·2 g.), m. p. 141° (Found : C, 62·6; H, 5·1; N, 11·0. $C_{21}H_{23}N,C_6H_3O_7N_3$ requires C, 62·6; H, 5·5; N, 10·8%). The *base*, regenerated from the picrate with sodium hydroxide, had b. p. 150—155°/0·13 mm. (Found : C, 86·8; H, 7·6; N, 4·9. $C_{21}H_{23}N$ requires C, 87·2; H, 7·9; N, 4·8%). The *methiodide* formed white prisms from acetone, m. p. 152° (Found : C, 60·9; H, 5·7; N, 3·5; I, 29·7. $C_{22}H_{26}NI$ requires C, 61·2; H, 6·0; N, 3·25; I, 29·5%).

By interaction of crude 3-bromo-1 : 4-diphenylbut-1-yne (prepared as described above from the alcohol and phosphorus tribromide) and piperidine, the same 3-piperidino-1 : 4-diphenylbut-1-yne was

obtained, b. p. 150—160°/0·15 mm., identified by its picrate, m. p. and mixed m. p. 141°, and its methiodide, m. p. and mixed m. p. 152°.

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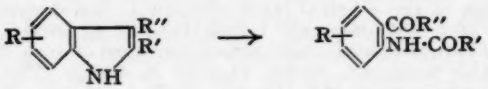
171. *Indoles. Part I. The* Bz-*Nitro*-2 : 3-*dimethylindoles and Their Use in Preparing Nitro*-2-*aminoacetophenones.*

By K. SCHOFIELD and R. S. THEOBALD.

The oxidation of the *Bz*-nitro-2 : 3-dimethylindoles to nitro-2-aminoacetophenones has been examined. It offers a preparative method for obtaining 3-nitro- and 5-nitro-2-aminoacetophenone. 4-*Nitro*- and 6-*nitro*-2 : 3-*dimethylindole* and 4-*nitro*- and 6-*nitro*-2-*aminoacetophenone* are described, and the nitration of *N*-acetyl-2 : 3-dimethylindole has been reinvestigated.

VARIOUS modes of oxidation of indole derivatives have been studied [the formation of indigo and related substances is well known, and among others the autoxidation to indole ethers is noteworthy (Oddo, *Gazzetta*, 1916, **46**, I, 323; 1920, **50**, II, 268; Taffoli, *Atti X° Congr. intern. Chim.*, 1939, **3**, 369; Plancher and Colacicchi, *Atti R. Accad. Lincei*, 1911, **20**, I, 453)], but relatively few examples are known of oxidative ring fission of the type



Jackson (*Ber.*, 1881, **14**, 885) obtained acetylanthranilic acid by the action of alkaline permanganate on 2-methylindole, and the formation of the same product through an intermediate ether by autoxidation in sunlight has been observed (Baudisch and Haschek, *Ber.*, 1916, **49**, 2579), but only recently has this type of ring opening been exploited to any extent. Witkop and his collaborators found that ozone converted indole into anhydrotris-(2-aminobenzaldehyde), whilst 2-methylindole in formamide solution gave 2-acetamidobenzaldehyde. Under similar conditions skatole, 2 : 3-dimethylindole, and 3-ethylindole were ozonised to give, respectively, 2-formamido- and 2-acetamido-acetophenone and 2-formamidopropiophenone. Besides ozone, perbenzoic and peracetic acids were used, and the reaction applied to certain alkaloid derivatives (Witkop and Graser, *Annalen*, 1944, **556**, 103; Witkop and Fiedler, *ibid.*, 1947, **558**, 91; Witkop, *ibid.*, 1947, **558**, 98). Koelsch, using chromic acid in acetic acid solution, obtained 5-bromo-2-benzoyl-*N*-acetylbenzanilide from 6-bromo-1-acetyl-2 : 3-diphenylindole (*J. Amer. Chem. Soc.*, 1944, **66**, 1983), and with the same reagent converted 2 : 4- and 2 : 6-dicarbethoxy-3-(2′-carbethoxyethyl)indole into ethyl β-(6-carbethoxy-2-ethoxalylaminobenzoyl)propionate and the 4-carbethoxy-compound respectively (*J. Org. Chem.*, 1943, **8**, 295). Plant and his co-workers have effected similar ring openings with this reagent, converting 1 : 6-diacetyl-2 : 3-dimethylindole into 2 : 5-diacetylacetanilide, and 1-acetyl-2 : 3-dimethylindole into 2-acetamidoacetophenone (Gaudion, Hook, and Plant, *J.*, 1947, 1631). The indole heterocycle has also been opened in the same sense by Plant (*J.*, 1940, 283, etc.) by the device of adding the elements of nitric acid to the indole C_2–C_3 double bond, and degrading the product with alkali. It will be noticed that in the oxidations with chromic acid mentioned above the *N*-acetyl derivatives of the indoles were used, except in the cases where the indole *Bz*-ring contained the strongly electron-attracting carbethoxy-group.

This oxidative fission of the indole heterocycle appeared to us to offer a possibly easy route to substituted 2-aminoacetophenones useful in various connections, more particularly in the present instance for the synthesis of 4-hydroxycinnolines (Schofield and Simpson, *J.*, 1945, 520, and other papers of the same series), and to analogous 2-aminobenzophenones, and in the present communication we describe its application to the preparation of all four isomeric nitro-2-aminoacetophenones. Hitherto the most readily available of these compounds has been 5-nitro-2-aminoacetophenone (Simpson *et al.*, *J.*, 1945, 646; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 405) but its preparation requires 2-aminoacetophenone, not very easily obtained in quantity, as starting material. This preparation yields small amounts of 3-nitro-2-aminoacetophenone as a minor product under certain conditions (Simpson, *J.*, 1947, 237), but no satisfactory preparative method was hitherto available for this compound. 4-*Nitro*- and 6-*nitro*-2-*amino*-

acetophenone have not previously been described, although Plant and Whitaker (*J.*, 1940, 283) mention the crude acetyl derivative of the former.

Ethyl methyl ketone *o*- and *p*-nitrophenylhydrazones have been used in the Fischer synthesis of 7- and 5-nitro-2 : 3-dimethylindole by Bauer and Strauss (*Ber.*, 1932, **65**, 308), and the second example has also been described by Plant and Tomlinson (*J.*, 1933, 955). We find the conditions described by the German workers to be preferable, and the yields of these indoles so obtained are 44% and 57%, respectively, based on the parent nitroanilines. The same authors (*loc. cit.*) also carried out the cyclisation of the corresponding *m*-nitrophenylhydrazone, isolating from the resulting mixture a product, m. p. 126°. From the same reaction Plant and Tomlinson (*loc. cit.*) obtained the second isomer, m. p. 142°. This second substance was identical with the compound formed by nitration and subsequent hydrolysis of 1-acetyl-2 : 3-dimethylindole, and Plant and Whitaker (*loc. cit.*) later proved it to be 6-nitro-2 : 3-dimethylindole. They further purified the compound isolated by Bauer and Strauss, raising its melting point to 130°, found that it depressed the melting point of their 6-nitro-compound, and thus concluded it to be 4-nitro-2 : 3-dimethylindole. In re-examining these results we found the conditions of Bauer and Strauss for the cyclisation of the *m*-nitrophenylhydrazone again to be preferable, giving 32% of mixed isomers based on *m*-nitroaniline. With a view to obtain as nearly as possible quantitative separation of each isomer present in the mixture, we investigated the possibility of separation by adsorption on alumina, a technique which proved successful in the closely related carbazole series (Barclay and Campbell, *J.*, 1945, 530). Adsorption from benzene, and elution with benzene–pyridine mixture gave almost quantitative recovery of two isomeric nitro-2 : 3-dimethylindoles, the least strongly adsorbed being a crimson compound, m. p. 172—173°, and the more strongly adsorbed an orange solid, m. p. 141—142°, the two occurring in the ratio 5 : 8, approximately. This result clearly rendered it necessary to orient the compounds afresh, both for the present purpose and as a check on the direction of nitration of 1-acetyl-2 : 3-dimethylindole as studied by Plant and Whitaker (*loc. cit.*).

As noted above, electron-attracting groups in the indole *Bz*-ring appear to render possible oxidative fission of the hetero-ring without the need for protecting the compound by acetylation. This proved to be the case with the nitro-2 : 3-dimethylindoles. By the action of chromic acid in acetic acid upon 5- and 7-nitro-2 : 3-dimethylindole, 5- and 3-nitro-2-acetamidoacetophenone were obtained in yields of 25% and 22% based on the parent nitroanilines. Clearly, the method, which is economical in time, is of great preparative value for these compounds, and in our experience is superior to previous methods. The nitro-2 : 3-dimethylindoles, m. p. 141—142° and 172—173°, originating from *m*-nitroaniline were likewise oxidised to isomeric nitro-2-acetamidoacetophenones, m. p. 126—127° and 143—144° respectively, and thence, by hydrolysis, provided the related 2-amino-ketones, m. p. 162—163° and 74—75°. The first of these, by diazotisation and reduction with hypophosphorous acid, gave *p*-nitroacetophenone, m. p. 81°, identified by hypochlorite oxidation to *p*-nitrobenzoic acid. To summarise, the Fischer cyclisation of methyl ethyl ketone *m*-nitrophenylhydrazone provides 4-nitro-, m. p. 172—173°, and 6-nitro-2 : 3-dimethylindole, m. p. 141—142°, in the approximate ratio of 5 : 8, from which may be obtained 6-nitro-, m. p. 74—75°, and 4-nitro-2-aminoacetophenone, m. p. 162—163°. The compound, m. p. 130°, previously assumed to be *4-nitro-2 : 3-dimethylindole* must have been impure.

The problem of the cyclisation of the arylhydrazones of unsymmetrical ketones has not been extensively investigated, and in most of the cases on record one product only seems to be formed (van Order and Lindwall, *Chem. Reviews*, 1942, **30**, 69). One exception is found in the ring closure of methyl ethyl ketone phenylhydrazone, which Korczynski, Brydowna, and Kierzek (*Gazzetta*, 1926, **56**, 903) report to give 2 : 3-dimethylindole and 2-ethylindole in the approximate ratio of 4 : 1. The present work shows that in the case of the nitrophenylhydrazones of methyl ethyl ketone the product isolated from the cyclisation contains substances arising from ring closure in one way only. Again, the case of Fischer cyclisation of *m*-substituted arylhydrazones does not appear to have received much attention from the point of view of determining the proportions of 4- and 6-substituted isomers formed. According to Hollins (" Synthesis of Nitrogen Ring Compounds," London 1924, p. 96) the reactive position in a *m*-substituted arylhydrazone is " probably that which is *para* to the substituent group." Steric considerations make this not unlikely (since Fischer indolisation appears to be independent of the electronic characteristics of substituents in the aryl nucleus) and it certainly received support in the present instance. However, Barclay and Campbell (*loc. cit.*) find the products from *cyclo*hexanone *m*-nitrophenylhydrazone to occur in equal proportions, though this does not appear to be so with the analogous *m*-bromo-compound, and indeed, in the example investigated by Koelsch (*loc. cit.*)

a larger yield of the 4-substituted indole than of the 6-isomer (3 : 2) was isolated. The significance of this last result is doubtful in view of the crystallisation processes used in purifying the substances, and in general, the precise determination of the proportion of isomers formed in such reactions is rendered difficult by the far from quantitative yields and the fact that the solubilities of the isomers in the cyclisation medium, if it be a liquid, are not necessarily the same.

We have repeated the nitration of 1-acetyl-2 : 3-dimethylindole according to Plant and Whitaker (*loc. cit.*), and find the product to be 6-nitro-1-acetyl-2 : 3-dimethylindole formed in 14% yield. The homogeneity of this product was established by hydrolysis to 6-nitro-2 : 3-dimethylindole which underwent no resolution on an alumina column.

Other examples of the type of oxidation reaction described are being investigated, especially its application to the formation of 2-aminobenzophenones, and will be described later, as will the cinnolines derived from these new aminoacetophenones.

Experimental.

(Melting points are uncorrected.)

Nitrophenylhydrazines.—The *o*- and *m*-compounds were obtained in yields of 72% and 65% respectively by the method of Muller *et al.* (*Helv. Chim. Acta*, 1937, **20**, 1468), whilst *p*-nitrophenylhydrazine resulted in 72% yield according to Vogel ("A Text-Book of Practical Organic Chemistry," London, 1948, p. 609).

Nitrophenylhydrazones.—Methyl ethyl ketone *o*-, m. p. 72—73° (95%), *m*-, m. p. 98—99° (84%), and *p*-nitrophenylhydrazone, m. p. 124—125° (91%), resulted when the ketone and hydrazine were heated in equivalent amounts for 1 hour at 95° and the product was crystallised from ethanol (Plant and Tomlinson, *J.*, 1933, 955).

Fischer Cyclisations.—7-Nitro-, m. p. 158—160° (44%), 5-nitro-, m. p. 184—185° (57%), and a mixture of 4- and 6-nitro-2 : 3-dimethylindole (32%) were obtained by heating the nitrophenylhydrazones (10 g.) with hydrochloric acid (100 c.c., *d* 1·18) for 4 hours at 95°, collecting the product, and washing it with hydrochloric acid. On a larger scale (*ca.* 50 g. of hydrazone) the yields from the *o*- and *m*-compounds fell to 28% and 26% respectively (yields are based on the corresponding nitroanilines) (Bauer and Strauss, *loc. cit.*)

Chromatographic Separation of 4- *and* 6-*Nitro*-2 : 3-*dimethylindole.*—A filtered solution of the crude mixture (15 g.) from the Fischer cyclisation of methyl ethyl ketone *m*-nitrophenylhydrazone in benzene (500 c.c.) was adsorbed on alumina (60 cm. × 3·5 cm. of type "H," supplied by Messrs. Peter Spence Ltd.), and the adsorbate developed with benzene until separation into a lower, orange band and an upper, red band occurred. The lower band was quickly eluted with benzene (2·89 g., m. p. 171—172°), and after a middle fraction had been collected (5·49 g., m. p. 125—130°), the remainder of the upper layer was washed out with benzene–pyridine (10 : 1) (5·65 g., m. p. 132—135°). The first fraction was homogeneous, and crystallisation from dilute ethanol gave crimson plates of 4-*nitro*-2 : 3-*dimethylindole*, m. p. 172—173° (Found : C, 63·10; H, 5·11. $C_{10}H_{10}O_2N_2$ requires C, 63·16; H, 5·26%). Similarly, 6-nitro-2 : 3-dimethylindole, m. p. 141—142°, was obtained from the third fraction in orange leaflets (Found : C, 62·98; H, 5·15%). Re-adsorption and elution of the middle fraction using benzene permitted complete separation, giving 2·49 g. more of the 4- and 2·98 g. more of the 6-compound. Thus the total yields of these were 5·38 g. and 8·63 g., respectively, an approximate ratio of 5 : 8.

3-*Nitro*-2-*aminoacetophenone.*—7-Nitro-2 : 3-dimethylindole (22 g.) in acetic acid (200 c.c.) was treated gradually with chromic anhydride (20 g.) in water (20 c.c.), the temperature not being allowed to rise above 40°. The solution was left overnight, diluted with water, and extracted with chloroform. The washed and dried (Na_2CO_3) extract left a sticky solid (13·7 g.) on concentration, which crystallised from benzene to give almost pure 3-nitro-2-acetamidoacetophenone, m. p. 151—152° (10·7 g., 42%). Hydrolysis (Simpson, *J.*, 1947, 237) gave 3-nitro-2-aminoacetophenone, m. p. 94—95° (7·7 g.). On a smaller scale (0·5 g.) the oxidation yielded 50% of the acetamido-compound (22% based on *o*-nitroaniline).

5-*Nitro*-2-*aminoacetophenone.*—In the same way 5-nitro-2 : 3-dimethylindole (9 g.) gave 5-nitro-2-acetamidoacetophenone (4·5 g. of once crystallised material, m. p. 139—141°, 43%), providing 5-nitro-2-aminoacetophenone (3·5 g.), m. p. 153—154°, on hydrolysis (Simpson *et al.*, *J.*, 1945, 646). On the smaller scale (1 g.) the yield of acetamido-compound was 45% (25% based on *p*-nitroaniline).

4-*Nitro*-2-*aminoacetophenone.*—Oxidation of 6-nitro-2 : 3-dimethylindole (3 g.) as above gave a sticky brown solid, which provided the acetamido-compound (0·9 g., 26%) on crystallisation from benzene. 4-*Nitro*-2-*acetamidoacetophenone* separated from dilute alcohol in pale yellow needles, m. p. 126—127° (Found : C, 54·62; H, 4·48. $C_{10}H_{10}O_4N_2$ requires C, 54·04; H, 4·53%). Hydrolysis of this compound (0·9 g.) by refluxing with alcohol (10 c.c.), concentrated hydrochloric acid (5 c.c.), and water (5 c.c.) on the steam-bath for ½ hour, followed by basification with ammonia, gave the free amine (0·7 g.). 4-*Nitro*-2-*aminoacetophenone* crystallised from dilute alcohol in fine orange needles, m. p. 162—163° (Found : C, 53·69; H, 4·43. $C_8H_8O_3N_2$ requires C, 53·33; H, 4·44%). This amine (0·2 g.) in acetic acid (2 c.c.) and sulphuric acid (1 c.c. of *ca.* 30N), was diazotised at 0° with powdered sodium nitrite (0·1 g.), and the solution treated with hypophosphorous acid (2 c.c. of 15%) after being diluted with iced water (10 c.c.). After standing overnight at 0° the solution was basified with sodium hydroxide and extracted with ether. The dried extract (Na_2SO_4) yielded *p*-nitroacetophenone (0·08 g.), m. p. 80—81° after crystallisation from dilute alcohol. This ketone (0·05 g.) was heated at 95° for 1 hour with sodium hydroxide solution (10 c.c. of 2N) and sodium hypochlorite prepared from sodium hydroxide (0·5 g.) in water (5 c.c.). Acidification with hydrochloric acid gave *p*-nitrobenzoic acid (0·02 g.), which

separated from water in colourless leaflets, m. p. 237—238°, alone and mixed with an authentic specimen.

6-*Nitro*-2-*aminoacetophenone*.—4-Nitro-2 : 3-dimethylindole (1 g.) on oxidation provided 0·35 g. (30%) of once crystallised (benzene) acetamido-compound. 6-*Nitro*-2-*acetamidoacetophenone* formed pale yellow needles, m. p. 143—144°, from aqueous ethanol (Found: C, 54·30; H, 4·67%). Hydrolysis of this substance (0·25 g.) with hydrochloric acid (10 c.c. of 6N) at 95° for ½ hour, followed by basification with ammonia gave 6-*nitro*-2-*aminoacetophenone* (0·20 g.), which separated in fine yellow needles, m. p. 74—75°, from dilute alcohol (Found: C, 53·23; H, 4·51%).

Nitration of 1-*Acetyl*-2 : 3-*dimethylindole*.—Nitration of the indole (4 g.) according to Plant and Whitaker (*loc. cit.*) gave 0·70 g. (14%) of product, m. p. 165—167°. One crystallisation from alcohol raised the m. p. to the constant value, 167—168°. Hydrolysis of the acetyl compound (0·5 g.) with alcoholic potash gave 6-nitro-2 : 3-dimethylindole (0·25 g.), m. p. 139—140°, which proved to be homogeneous when applied to an alumina column in benzene solution, giving quantitative recovery on elution.

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172. *Polycyclic Aromatic Amines. Part II.*

By G. M. BADGER and A. R. M. GIBB.

Further work on the synthesis of compounds analogous to the cancer-producing amines is reported. 1 : 2-Benzanthraquinone has been brominated in the 4′-position, and the product converted into 4′-*amino*-1 : 2-*benzanthracene*, which has also been obtained from 4′-nitro-1 : 2-benzanthraquinone. 1′ : 9-*Imino*-1 : 2-*benzanthracene* has been prepared from 1′-nitro-1 : 2-benzanthraquinone. 1 : 2-Benzanthracene-10-carboxylic acid has been converted into the 10-amino-compound by the Schmidt reaction, which, however, failed with 1 : 2-benzanthracene-4′-carboxylic acid and also with 1 : 2-benzanthracene-4-carboxylic acid. The latter has been prepared in satisfactory yield from 4 : 10-oxalyl-1 : 2-benzanthracene.

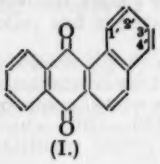
It has also been found that 1 : 2-benz-10-anthranylglyoxylic acid chloride is readily degraded to 1 : 2-benzanthracene-10-carboxylic acid by hydrolysis with sodium hydroxide. This finding is discussed in relation to the mechanism of the formation of carboxylic acid derivatives in Friedel–Crafts reactions with oxalyl chloride.

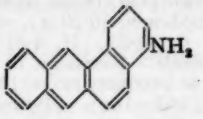
As it is important to determine the relationship, if any, between the carcinogens of the polycyclic aromatic hydrocarbon type and the cancer-producing amines such as 2-aminofluorene, the synthesis of certain aminobenzanthracenes has been undertaken. In Part I of this series, Badger (*J.*, 1948, 1756) has described the preparation of 2′-amino-1 : 2-benzanthracene, and the present paper describes further work in this field.

1 : 2-Benzanthraquinone (I) is known to undergo substitution in a variety of positions depending on the reagent and the experimental conditions. It has been sulphonated in the 4′-position at ordinary temperatures (Sempronj, *Gazzetta*, 1939, **69**, 448; Cason and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2681), and in the 2′-position at elevated temperatures (Joffe and Fedorova, *J. Gen. Chem. Russia*, 1941, **11**, 619; Badger, *J.*, 1947, 940). Furthermore, from the products of the nitration of benzanthraquinone, Scholl (*Ber.*, 1911, **44**, 2370) isolated 1′-nitro-1 : 2-benzanthraquinone and an isomeric nitrobenzanthraquinone which he regarded as the 4′-derivative.

It has now been found that benzanthraquinone is readily brominated in the 4′-position, the product being identical with a specimen of 4′-bromo-1 : 2-benzanthraquinone, of established constitution, prepared by the method of Johnson, Weinmayr, and Adams (*J. Amer. Chem. Soc.*, 1932, **54**, 3289) by cyclisation of *o*-(5′-bromo-1′-naphthoyl)benzoic acid. With ammonium hydroxide under pressure, this bromobenzanthraquinone has been converted into 4′-*amino*-1 : 2-*benzanthraquinone*, which, on reduction in the usual manner, gave 4′-*amino*-1 : 2-*benzanthracene* (II). The aminobenzanthraquinone, m. p. 255—257°, seemed not to be identical with the aminobenzanthraquinone, m. p. 215°, which Scholl (*loc. cit.*) obtained on reduction of his supposed 4′-nitro-1 : 2-benzanthraquinone, and in view of this discrepancy, the nitration of benzanthraquinone has been re-investigated. In agreement with Scholl, a mixture of nitrobenzanthraquinones was obtained, and 1′-nitro-1 : 2-benzanthraquinone was readily isolated in a pure condition. This product has been reduced to 1′ : 9-*imino*-1 : 2-*benzanthracene* (III) by the two-stage process frequently used for the reduction of benzanthraquinones (Badger and Cook, *J.*, 1939, 802), and the isolation of this compound confirms the orientation of the 1′-nitro-

derivative. In spite of repeated attempts, a completely pure specimen of the isomeric nitrobenzanthraquinone could not be obtained. Reduction of the partly purified material, however, with sodium sulphide, gave 4′-amino-1 : 2-benzanthraquinone, identical with the specimen obtained as above from the bromo-compound. The identity of the two specimens


(I.)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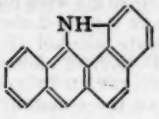
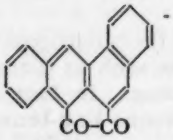

(III.)

was also confirmed by a comparison of the *acetyl* derivatives. It must be concluded, therefore, that although Scholl's orientation for the aminobenzanthraquinone is correct, his m. p. is in error.

1 : 2-Benzanthracene-10-carboxylic acid is readily available (Dansi, *Gazzetta*, 1937, **67**, 85; Badger and Cook, *J.*, 1940, 409; this paper), and it has been converted into the known 10-amino-1 : 2-benzanthracene (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1938, **60**, 1893; Fieser and Creech, *ibid.*, 1939, **61**, 3502) by the Schmidt reaction. In view of this success, it was thought that the 4-amino-compound might become available through 1 : 2-benzanthracene-4-carboxylic acid. This acid had been obtained as a by-product by Cook (*J.*, 1931, 2524) and a more convenient synthesis was therefore desirable. 4 : 10-Oxalyl-1 : 2-benzanthracene (IV) (cf. Dansi, *loc. cit.*) was prepared by an improved method from benzanthracene and oxalyl chloride, and this was oxidised with sodium dichromate to 1 : 2-benzanthraquinone-4-carboxylic acid (V) and reduced to the desired 1 : 2-benzanthracene-4-carboxylic acid (VI), in reasonable yield. Both acids have been identified by comparison with authentic specimens, and it will be noted that this work confirms the structure of the 4 : 10-oxalyl-1 : 2-benzanthracene. The Schmidt reaction failed with 1 : 2-benzanthracene-4-carboxylic acid, however, and although several other attempts had been made to degrade this acid to the amino-compound, no success has yet been achieved. The Schmidt reaction also failed with 1 : 2-*benzanthracene-4′-carboxylic acid*, which has been prepared from 4′-bromo-1 : 2-benzanthraquinone through 4′-*cyano*-1 : 2-*benzanthraquinone* and 1 : 2-*benzanthraquinone-4′-carboxylic acid*.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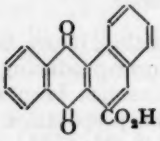
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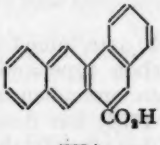
(VI.)

The Friedel–Crafts reaction with oxalyl chloride is of peculiar interest. Depending on the compound attacked, and on the experimental conditions, the product may be a ketone, a diketone, a carboxylic acid, or a mixture of two or more of these products. Furthermore, in particular cases, the ketones and diketones may be either uni- or bi-molecular. With certain compounds, oxalyl chloride provides the best method for the introduction of a carboxylic acid grouping. It is significant that glyoxylic acids seem never to be obtained, although these compounds are often readily available if " chloro-oxalic ester " is used in place of oxalyl chloride.

Oxalyl chloride is not a stable substance, and in the presence of aluminium chloride it is slowly decomposed into carbon monoxide and carbonyl chloride (Staudinger, *Ber.*, 1908, **41**, 3558). It has long been supposed (see Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," 1941) that the formation of monoketones, and of carboxylic acids, in Friedel–Crafts reactions with oxalyl chloride is due to this decomposition into carbonyl chloride which subsequently reacts with the aromatic component. As is well known, this substance does react with a variety of aromatic compounds to give monoketones and carboxylic acids. According to Staudinger (*Ber.*, 1912, **45**, 1594), whether Friedel–Crafts reactions with oxalyl chloride give rise to mono- or to di-ketones depends on the velocity of individual reactions: if the aromatic component is reactive, it combines with oxalyl chloride more rapidly than the latter is decomposed into carbon monoxide and carbonyl chloride, and a diketone is formed. This conclusion is illustrated by the fact that, although benzene reacts with oxalyl chloride to give benzoic acid and benzophenone (Staudinger, 1908, *loc. cit.*), yet anisole reacts rapidly to give anisil, in good yield (Staudinger, Goldstein, and Schlenker, *Helv. Chim. Acta*, 1921, **4**, 342).

Furthermore, oxalyl bromide, which is more stable than oxalyl chloride, reacts with benzene to give benzophenone and some benzil (Staudinger, 1912, *loc. cit.*).

Although the decomposition of oxalyl chloride into carbonyl chloride, and the subsequent condensation of this reagent with the aromatic component is without doubt the explanation for the formation of monoketones and, in some cases, for the formation of carboxylic acid, it seems that this is not the *only* mechanism by which carboxylic acids may be formed in this reaction. It had been observed (i) that the use of a large excess of aluminium chloride in the condensation of benzanthracene with oxalyl chloride does not result in an increased yield of carboxylic acid, as might be expected if the excess of aluminium chloride promoted the decomposition of oxalyl chloride into carbonyl chloride; and (ii) that an attempt to cyclise 1 : 2-benzanthranyl-10-glyoxylic acid chloride to 4 : 10-oxalyl-1 : 2-benzanthracene (IV) resulted in the isolation, in reasonable yield, of 1 : 2-benzanthracene-10-carboxylic acid. It therefore seemed likely that formation of carboxylic acids in Friedel–Crafts reactions with oxalyl chloride might, in some cases, be due to the degradation, by hydrolysis, of glyoxylic acid chloride formed as intermediate. This supposition is supported by the fact, mentioned above, that glyoxylic acids are never obtained in Friedel–Crafts reactions with oxalyl chloride, and it has been confirmed by the observation that 1 : 2-benz-10-anthranylglyoxylic acid chloride is hydrolysed and degraded to 1 : 2-benzanthracene-10-carboxylic acid by boiling for a few minutes with dilute sodium hydroxide. This observation is clearly related to the fact that oxalyl chloride is decomposed by water to hydrogen chloride, carbon monoxide, and carbon dioxide, and that no oxalic acid is formed under these conditions (Staudinger, 1908, *loc. cit.*).

It seems probable that this degradation of a glyoxylic acid chloride to a carboxylic acid, simply by hydrolysing with alkali, will prove to be of general application, and experiments to test this assumption are planned.

Badger and Cook (*J.*, 1940, 409) observed that when 1 : 2-benz-10-anthranylglyoxylic acid was submitted to the action of red phosphorus and hydriodic acid, some benzanthracene was formed as well as the desired acetic acid derivative. An attempt to carry out the reduction by the modified Kishner–Wolff method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) resulted in only a trace of the desired acid, almost the whole of the material being converted into benzanthracene. Indeed, benzanthracene was obtained when the glyoxylic acid was heated with potassium hydroxide in glycol, alone.

Experimental.

4′-Bromo-1 : 2-benzanthraquinone.—A mixture of 1 : 2-benzanthraquinone (2·6 g.), acetic acid (30 c.c.), and bromine (2 c.c.) was boiled under reflux for 4 hours. After cooling, the crystalline product was collected, and recrystallised from acetic acid, in which it is sparingly soluble (yield, 2·6 g.). 4′-Bromo-1 : 2-benzanthraquinone formed long yellow needles, m. p. 230—232° (lit. 231—232°) (Found: C, 64·2; H, 2·7. Calc. for $C_{18}H_9O_2Br$: C, 64·1; H, 2·7%). The m. p. was not depressed by admixture with a specimen prepared by brominating naphthoylbenzoic acid, followed by cyclisation (Johnson, Weinmayr, and Adams, *loc. cit.*).

4′-Bromo-1 : 2-benzanthracene.—The above bromobenzanthraquinone (1·5 g.) was heated under reflux for 1 hour with acetic acid (150 c.c.), concentrated hydrochloric acid (15 c.c.), and stannous chloride (3 g.). The crude product obtained by the addition of water was immediately reduced further by 3 hours' boiling with zinc dust (10 g.) and 2N-sodium hydroxide (100 c.c.). *4′-Bromo-1 : 2-benzanthracene* (1·4 g.) formed colourless plates from acetic acid, m. p. 210—211° (Found: C, 70·2; H, 3·6. $C_{18}H_{11}Br$ requires C, 70·4; H, 3·6%).

4′-Cyano-1 : 2-benzanthraquinone.—A suspension of the above bromobenzanthraquinone (2 g.) and cuprous cyanide (2 g.) in benzyl cyanide (10 c.c.) was heated at 180—200° for 6 hours. The cooled mixture, after being warmed for ½ hour on the steam-bath with a little concentrated hydrochloric acid, was treated with a little benzene and, after cooling, collected. The solid so obtained was recrystallised from benzyl cyanide and then from tetrahydrofurfuryl alcohol. *4′-Cyano-1 : 2-benzanthraquinone* (1·1 g.) formed fluffy yellow needles, m. p. 297—299°, after darkening (Found: C, 80·5; H, 3·3. $C_{19}H_9O_2N$ requires C, 80·6; H, 3·2%).

1 : 2-Benzanthraquinone-4′-carboxylic Acid.—The above cyanobenzanthraquinone (1 g.) was hydrolysed by 20-hours' boiling with a solution of acetic acid (100 c.c.) and 65% sulphuric acid (25 c.c.) (cf. Newman and Orchin, *J. Amer. Chem. Soc.*, 1939, **61**, 244). *1 : 2-Benzanthraquinone-4′-carboxylic acid*, isolated by addition of water to the hot solution, and recrystallised from acetic acid, formed small yellow needles, m. p. 301—303° (decomp.) (0·75 g.) (Found: C, 75·7; H, 3·2. $C_{19}H_{11}O_3N$ requires C, 75·5; H, 3·3%).

1 : 2-Benzanthracene-4′-carboxylic acid.—The above carboxybenzanthraquinone was reduced in the usual manner with zinc dust and boiling dilute ammonia. *1 : 2-Benzanthracene-4′-carboxylic acid* formed small orange needles, m. p. 286° (Found: C, 83·8; H, 4·5. $C_{19}H_{12}O_2$ requires C, 83·8; H, 4·4%). No non-acidic material was obtained when this compound was submitted to the action of hydrazoic acid in the same way as for the 10-isomer (below).

Nitration of Benzanthraquinone.—Nitration of benzanthraquinone by Scholl's method (*loc. cit.*), and separation of the isomers with boiling chloroform, readily gave crude 1′- and 4′-nitro-1 : 2-benzanthra-

quinone. The former was obtained as glistening yellow blades, m. p. 286—288° (lit. 277—278°) after 12 recrystallisations from nitrobenzene. The 4′-isomer could not be obtained completely pure, but a crude product, m. p. 220—230°, was easily obtained, and was found suitable for further work.

4′-Amino-1 : 2-*benzanthraquinone*.—(i) A mixture of bromobenzanthraquinone (0·5 g.), cuprous chloride (0·5 g.), ammonium hydroxide (12 c.c.; *d* 0·880), and dioxan (3 c.c.) was heated in a sealed tube at 180—190° for 48 hours. The product, *4′-amino*-1 : 2-*benzanthraquinone* (0·3 g.), was recrystallised from nitrobenzene, and then from toluene, and formed dark red prisms, m. p. 255—257° (Found: C, 79·3; H, 3·9. $C_{18}H_{11}O_2N$ requires C, 79·1; H, 4·0%). The *acetyl* derivative, prepared from the amine with acetic anhydride and sodium acetate, formed yellow needles, m. p. 289—290°, from acetic acid (Found: C, 76·0; H, 4·1. $C_{20}H_{13}O_3N$ requires C, 76·1; H, 4·2%).

(ii) 4′-Nitro-1 : 2-benzanthraquinone (2 g.) was made into a thin paste with sodium sulphide (10 g.) and water, and added to 200 c.c. of boiling water, and the whole boiled for a further ½ hour. The crude aminobenzanthraquinone (1·6 g.) was collected, and recrystallised from toluene. After 3 recrystallisations, it had m. p. 254°, not depressed by admixture with 4′-amino-1 : 2-benzanthraquinone prepared as described above. The acetyl derivatives were also shown to be identical by direct comparison.

4′-Amino-1 : 2-*benzanthracene*.—The above aminobenzanthraquinone was reduced with zinc dust and dilute ammonium hydroxide, in the usual way. *4′-Amino*-1 : 2-*benzanthracene*, recrystallised from benzene, formed yellow plates, m. p. 199—201° (Found: C, 88·9; H, 5·4. $C_{18}H_{13}N$ requires C, 88·9; H, 5·35%). The acetyl derivative proved to be unstable: each recrystallisation gave some insoluble material, and a pure specimen could not be obtained. The *benzoyl* derivative formed colourless silky needles, m. p. 276—277°, from acetone (Found: C, 86·5; H, 5·05. $C_{25}H_{17}ON$ requires C, 86·4; H, 4·9%).

1′ : 9-*Imino*-1 : 2-*benzanthracene*.—1′-Nitro-1 : 2-benzanthraquinone (1 g.) was boiled for 1 hour with acetic acid (50 c.c.), hydrochloric acid (10 c.c.), and stannous chloride (5 g.). Water was added, and after standing for 1 hour, the solid was collected and immediately boiled with zinc dust (5 g.) and 2N-sodium hydroxide (50 c.c.) for 3 hours. The solid was dried, extracted with benzene, and the solvent removed. The product, after sublimation at 200°/0·1 mm., was recrystallised from benzene. The dilute solution had an intense blue fluorescence in daylight. 1′ : 9-*Imino*-1 : 2-*benzanthracene* formed pale yellow crystals, m. p. 217·5—219·5° (Found: C, 89·8; H, 4·3. $C_{18}H_{11}N$ requires C, 89·6; H, 4·6%). The *picrate* formed dark brown needles, from benzene, m. p. 191—192° (Found: C, 61·4; H, 3·0. $C_{24}H_{14}O_7N_4$ requires C, 61·3; H, 3·0%).

10-*Amino*-1 : 2-*benzanthracene*.—A mixture of 1 : 2-benzanthracene-10-carboxylic acid (1 g.) in chloroform (50 c.c.) and concentrated sulphuric acid (15 c.c.) was treated, at 40—50°, with sodium azide (2 g.) in small portions, with hand stirring, during 1 hour. The mixture was poured into water, filtered, and the solid washed with water, followed by hot dilute sodium carbonate, and then hot water. The product, 10-amino-1 : 2-benzanthracene, was recrystallised from benzene–light petroleum (b. p. 60—80°), and formed yellow plates (0·35 g.), m. p. 174·5—175·5°, in agreement with the literature (Found: C, 89·1; H, 5·5. Calc. for $C_{18}H_{13}N$: C, 88·9; H, 5·35%). The *acetyl* derivative formed fine colourless needles, from acetic acid, m. p. 276·5—277·5° (Found: C, 84·0; H, 5·1. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·3%).

2′-*Acetamido*-1 : 2-*benzanthraquinone*.—2′-Amino-1 : 2-benzanthraquinone (Part I) was acetylated by brief boiling with acetic anhydride and sodium acetate. The *acetamido*-compound formed small orange-yellow prisms, m. p. 286—288°, from chlorobenzene (Found: C, 76·3; H, 4·3. $C_{20}H_{13}O_3N$ requires C, 76·1; N, 4·2%).

2′-*Acetamido*-1 : 2-*benzanthracene*.—The *acetyl* derivative of 2′-amino-1 : 2-benzanthracene (Part I) formed colourless needles, m. p. 235—236°, from methanol (Found: C, 84·3; H, 5·25. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·3%).

4 : 10-*Oxalyl*-1 : 2-*benzanthracene*.—The following procedure was found to be superior to that used by Dansi (*loc. cit.*). A mixture of 1 : 2-benzanthracene (20 g.) and oxalyl chloride (12·5 g.) in dry tetrachloroethane (250 c.c.) was cooled in ice and treated with aluminium chloride (56 g.) in small portions, with stirring. After 2 hours the mixture was warmed on the steam-bath for 8 hours. The residue obtained on removal of the tetrachloroethane in steam was extracted with boiling sodium carbonate, and the insoluble material then extracted with boiling acetic acid. Acidification of the sodium carbonate solution gave 1 : 2-benzanthracene-10-carboxylic acid (0·2 g.), identified, after recrystallisation, by comparison with an authentic specimen. The yield of 4 : 10-oxalyl-1 : 2-benzanthracene, obtained from the acetic acid solution, was 8·0 g., and a black insoluble material (9 g.), which was not further examined, was also obtained. Similar results were obtained when the above reaction was repeated using carbon disulphide as solvent; but more acid and less ketone were isolated.

1 : 2-*Benzanthraquinone*-4-*carboxylic Acid*.—Finely powdered oxalylbenzanthracene (8 g.), in boiling glacial acetic acid (300 c.c.), was treated with a solution of sodium dichromate (40 g.) in 80% acetic acid (100 c.c.) during 1 hour. After refluxing for a further hour, the solution was filtered (to remove a little unchanged ketone), evaporated to small bulk under reduced pressure, and poured into water. The product was extracted with boiling sodium carbonate solution, from which, on acidification, 1 : 2-benzanthraquinone-4-carboxylic acid (4 g.) was obtained. After recrystallisation from acetic acid it had m. p. 294—296°, not depressed by admixture with an authentic specimen. The residue (3·5 g.), insoluble in boiling sodium carbonate, purified by sublimation in a high vacuum and recrystallised from acetic acid, was identified as 1 : 2-benzanthraquinone by comparison with an authentic specimen. The acid was further identified by reduction, with zinc dust and boiling dilute ammonium hydroxide, to 1 : 2-benzanthracene-4-carboxylic acid, which formed yellow needles, m. p. 276—278°, not depressed by admixture with an authentic specimen, m. p. 281—282°. No non-acidic material was obtained when this acid was submitted to the Schmidt reaction as described for the 10-isomer.

Conversion of 1 : 2-*Benz*-10-*anthranylglyoxylic Acid into* 1 : 2-*Benzanthracene*-10-*carboxylic Acid*.—In an attempt to convert the glyoxylic acid into oxalylbenzanthracene by conversion into the acid chloride, and treatment with stannic chloride in benzene, the chief product isolated was 1 : 2-benzanthracene-10-carboxylic acid. The following procedure was also found to effect the degradation. 1 : 2-Benz-10-anthranylglyoxylic acid (0·4 g.) was boiled for ¼ hour with excess of thionyl chloride, and the excess then

removed in a vacuum, on the steam-bath. The solid product was boiled for ½ hour with dilute sodium hydroxide, and the solution filtered and acidified. The acid, recrystallised from acetic acid, formed small needles, m. p. 218—220°, not depressed by admixture with 1 : 2-benzanthracene-10-carboxylic acid.

2-(2′-*Methoxybenzoyl*)-1-*naphthoic Acid*.—In another paper, Badger (*J.*, 1947, 940) described the interaction of *o*-anisylmagnesium bromide and 1 : 2-naphthalic anhydride, and the isolation, after purification through the acetoxy-lactone, of an acid which was designated 2-*o*-methoxybenzoyl-1-naphthoic acid. The prior use of this reaction by Newman and Wise (*J. Amer. Chem. Soc.*, 1941, **63**, 2109) was inadvertently overlooked. These workers purified the crude acid by fractional crystallisation, and isolated two isomeric acids, and determined their structure. Through the courtesy of Professor Newman, who kindly supplied specimens of his acids, it has been possible to confirm, by mixed m. p. determinations, that the acid described by Badger does, in fact, have the structure assigned to it.

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173. *Reaction Mechanism of the Oxidation of Hydrogen Bromide.*

By ZOLTÁN SZABÓ and ELIZABETH KISS.

Experiments have been made to elucidate the mechanism of hydrogen bromide oxidation in the temperature range 490—635°. The velocity constants depend on the total pressure. Corresponding to this fact a reaction scheme is suggested, the accuracy of which is shown by the constancy of the computed velocity constants. The activation energy and the steric factor proved to be plausible values. With the aid of these quantities the calculated velocity constants agree quite satisfactorily with the empirical ones.

HITHERTO the only publications relating to this reaction have been mainly of a qualitative nature (Ballard, *Ann. Chim. Phys.*, 1826, **32**, 349; *Pogg. Ann.*, 1826, **8**, 321; Richardson, *J.*, 1887, **51**, 804), the work of Berthelot (*Compt. rend.*, 1878, **87**, 670; *Ann. Chim. Phys.*, 1879, **16**, 446) and Abel (Abegg's "Handbuch," Bd. IV, 2, 5, 276) not being of sufficient accuracy. In Harteck and Kopsch's experiments (*Z. Elektrochem.*, 1930, **36**, 715) the oxidation was effected by oxygen *atoms*, so was not relevant to our work. We therefore investigated the reaction by a modern technique.

EXPERIMENTAL.

Apparatus.—The reactants were mixed in a vessel of resistance glass, and the pressure change of the reaction $4HBr + O_2 = 2H_2O + 2Br_2$ was measured by a Bodenstein quartz spiral manometer, used as a null instrument. The reaction vessel was separated from the other parts of the apparatus by a Bodenstein glass valve. The connexion between the resistance glass, the normal glass, and the quartz tube was made by a ground-glass joint, which was also secured by sealing wax. The vessel was heated in an electric furnace of high heat capacity, and temperature was regulated by rheostats and checked by an electric pyrometer. The gases were kept in stock vessels, which led into the common pipe of the glass valve. The apparatus was exhausted by a mercury-diffusion pump.

Preparation of Gases.—The hydrogen bromide was prepared by Fileti's method (*Gazzetta*, 1891, **21**, 64). The evolved hydrogen bromide was scrubbed on glass beads covered with red phosphorus, suspended in a concentrated solution of hydrogen bromide, then conducted through six freezing-out tubes, the temperatures of which were arranged at intervals from −20° to −80°, so as to free it from the last traces of water. The pure gas condensed in the final tube was distilled into the stock vessel, the first and the last fraction being rejected.

The oxygen, from a cylinder, was purified by Stock and Ritter's method (*Z. physikal. Chem.*, 1926, **124**, 210). The gas was conducted through concentrated alkali, then over granulated calcium chloride and phosphoric oxide. The nitrogen was led over heated copper and through concentrated potassium hydroxide, then over calcium chloride and phosphoric oxide to free it from traces of water.

In an experiment the order of introduction of the gases was hydrogen bromide, nitrogen, and oxygen.

Results.—At 166° no reaction was detectable, and between 345° and 435° it was very slow, so we conducted experiments at 490°, 520°, 550°, 560°, 575°, 605°, and 635°.

As the simplest mechanism of the oxidation we assumed the following sequence (k_1, k_2, and k_3 being the velocity constants) :

$$HBr + O_2 = HOOBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_1$$

$$HOOBr + HBr = 2HOBr \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_2$$

$$HOBr + HBr = H_2O + Br_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad k_3$$

From Bodenstein's principle of the stationary concentration of intermediate products, this leads to

$$-d[HBr]/dt = 3k_1[HBr][O_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The velocity constant was calculated from the equation $dx/dt = k(a - x_1)(b - x_2)$ from point to point. The measured constant, k, would therefore be equal to $3k_1$.

The course of some typical experiments is shown in Table I. The velocity constants thus obtained were reasonably constant for any one experiment (although decreasing slightly) but they rose rapidly with decreasing initial pressure, as shown in col. 4 of Table II. This inhibitory influence of total pressure could be interpreted by insertion of another stage involving a slackening by any gas molecule M:

$$HOOBr + M = HBr + O_2 + M \ldots \text{ velocity constant } k_1'.$$

This leads to the equation

$$-\frac{d[HBr]}{dt} = \frac{3k_1[HBr][O_2]}{1 + k_1'[M]/k_2[HBr]} \quad \ldots\ldots\ldots\ldots \quad (2)$$

Calculation from this formula is complicated because k_1'/k_2 occurs in the denominator, but by trial, a value of 6 for this ratio was found to lead to satisfactory constancy (see col. 5, Table II). However, this value was independent of temperature, and a similar phenomenon is to be found in the combination of hydrogen and bromine.

TABLE I.

Experiments at 575°.

Time. mins.	Press., mm.	Δp.	$\Delta p/\Delta t$.	$3k_1\times10^4$. from (1).	$3k_1\times10^3$. from (2).	Time, mins.	Press., mm.	Δp.	$\Delta p/\Delta t$.	$3k_1\times10^4$. from (1).	$3k_1\times10^3$. from (2).
			No. 50. $[O_2]$ = 40·0 mm.; [HBr] = 213·0 mm.								
0	253	—	—	—	—	21	233	20	0·50	1·9	2·2
3	247	6	2·0	3·1	2·75	37	228	25	0·31	1·8	2·4
6	243	10	1·3	2·6	2·5	45	226	27	0·25	1·8	2·5
10	239	14	1·0	2·45	2·5	55	224	29	0·20	1·9	2·8
15	236	17	0·6	1·8	1·9	72	221	32	0·176	2·6	(4·3)
			No. 52. $[O_2]$ = 203·0 mm.; [HBr] = 104·0 mm.								
0	307	—	—	—	—	25	289·5	17·5	0·214	0·34	1·8
3	299	8	2·67	1·9	4·9	35	288	19	0·150	0·29	1·8
6	296·5	10·5	0·83	0·70	2·1	45	286·5	20·5	0·150	0·37	3·0
10	293	14	0·87	0·97	3·6	55	286	21	0·10	0·31	2·9
18	291	16	0·25	0·33	1·5	65	284	23	0·15	0·09	(9·9)
			No. 55. $[O_2]$ = 40·0 mm.; [HBr] = 122·3 mm.								
0	162·3	—	—	—	—	20	148·8	13·5	0·283	1·6	2·2
3	155·3	7·0	2·3	7·5	(8·1)	32	146·3	16·0	0·208	1·5	2·4
5	153·7	8·6	0·8	2·9	3·3	43	144·3	18·0	0·181	1·6	3·0
8	152·5	9·8	0·4	1·6	1·9	55	142·7	19·6	0·133	1·5	3·0
14	150·5	11·8	0·33	1·6	2·0	71	140·8	21·5	0·118	1·5	(3·7)
			No. 175. $[O_2]$ = 122·9 mm.; [HBr] = 128·8 mm.								
0	251·7	—	—	—	—	20	229·5	22·2	0·340	0·84	3·0
2	242·2	9·5	4·75	4·6	(7·8)	28	227·3	24·4	0·275	0·89	4·0
5·5	236·8	14·9	1·54	2·1	(4·4)	40	225·9	25·8	0·117	0·47	2·5
8	235·0	16·7	0·72	1·1	2·6	51	225·1	26·6	0·073	0·34	2·1
11	233·1	18·6	0·63	1·1	3·0	70	223·5	28·2	0·084	0·56	(4·7)
15	231·2	20·5	0·47	1·0	3·0						
			No. 63. O_2 = 80·5 mm.; HBr = 81·6 mm.; N_2 = 160·7 mm.								
0	322·8	—	—	—	—	25	311·6	11·2	0·186	0·73	3·8
3	319·0	3·8	1·27	2·5	(7·4)	33	310·7	12·1	0·113	0·50	2·8
7	316·2	6·6	0·70	1·7	(6·1)	45	309·8	13·0	0·075	0·38	2·4
12	314·3	8·5	0·38	1·1	(4·5)	60	308·7	14·1	0·073	0·44	3·25
18	312·9	9·9	0·23	0·79	3·6	110	307·4	15·4	0·026	0·20	1·9
			No. 66. O_2 = 29·6 mm.; HBr = 150·0 mm.; N_2 = 119·4 mm.								
0	299·0	—	—	—	—	32	285·5	13·5	0·200	1·3	2·4
3	295·2	3·8	1·27	3·6	(5·1)	45	283·7	15·3	0·138	1·1	2·2
7	293·8	5·2	0·35	1·1	1·6	60	282·1	16·9	0·106	1·0	2·2
11	291·2	7·8	0·65	2·5	3·9	75	280·0	19·0	0·140	1·8	4·2
16	289·0	10·0	0·44	2·0	3·4	100	278·0	21·0	0·080	1·4	3·7
22	287·5	11·5	0·25	1·3	2·3	140	276·6	22·4	0·035	0·80	2·3

Note to Table.—The first, and sometimes the second, value of the velocity constants was higher than the later ones. We could not find any reason for this. Later, the process became stabilized and the velocity constants became suitably constant for one experiment. For the calculation of the mean values of the velocity constant only these stabilized values were taken. In Tables II and III the relation between the corresponding partial pressures and the mean velocity constants cannot be examined exactly, because the partial pressures given are initial values. The velocity constants in the tables were only calculated after the second or third readings, when the partial pressures, especially in the case of HBr, differ already considerably from the initial values. The strict validity of formula (2), as is shown by the experiments cited, refers only to this stabilized zone.

TABLE II.

Experiments at 575° (*concentrations in mm. of* Hg).

p_{O_2}.	p_{HBr}.	Total press.	$3k_1\times10^4$ from (1).	$3k_1\times10^3$ from (2).	p_{O_2}.	p_{HBr}.	Total press.	$3k_1\times10^4$ from (1).	$3k_1\times10^3$ from (2).
258·6	60·0	318·6	0·18	2·8	40·0	122·3	162·3	1·55	2·6
203·0	104·0	307·0	0·33	2·4	142·5	75·1	217·6	0·58	2·2
122·9	128·8	251·7	0·79	2·9	40·0	213·0	253·0	1·85	2·4
121·0	118·0	239·0	0·89	2·7	41·8	157·3	199·1	1·93	2·4
100·1	106·4	206·5	1·1	3·3	118·7	293·7	412·4	1·55	3·3
102·0	97·0	199·0	1·2	3·2	34·2	115·0	149·2	1·62	2·25
56·7	112·5	169·2	1·4	2·9					

TABLE III.

Experiments at 575° (*concentrations in mm. of* Hg).

p_{O_2}.	p_{HBr}.	p_{N_2}.	Total press.	$3k_1\times10^4$ from (1).	$3k_1\times10^3$ from (2).	p_{O_2}.	p_{HBr}.	p_{N_2}.	Total press.	$3k_1\times10^4$ from (1).	$3k_1\times10^3$ from (2).
46·6	65·3	264·1	376·0	0·39	2·5	29·6	150·0	119·4	299·0	1·51	2·8
80·5	81·6	160·7	322·8	0·69	2·9	50·0	202·5	98·4	350·9	1·03	2·2
122·0	62·6	119·7	304·3	0·65	3·5	42·1	158·9	315·2	516·2	0·91	3·7
56·0	99·6	99·6	255·2	0·95	2·6	50·2	200·3	99·1	349·6	1·56	3·4
59·4	119·8	59·7	238·9	1·62	2·9						

TABLE IV.

Experiments at 635° (*concentrations in mm. of* Hg).

p_{O_2}.	p_{HBr}.	p_{N_2}.	Total press.	$3k_1\times10^3$ from (2).	p_{O_2}.	p_{HBr}.	p_{N_2}.	Total press.	$3k_1\times10^3$ from (2).
51·4	143·5	—	194·9	11·0	57·1	193·0	94·8	344·9	4·5
38·9	91·2	109·9	240·0	12·7	61·7	54·0	291·8	406·5	38·1
260·4	187·6	—	248·0	7·7	60·9	183·2	—	244·1	8·7
200·8	106·4	—	307·2	13·7	177·4	88·6	—	266·0	12·1
104·2	102·3	98·6	324·9	9·51	101·8	103·0	—	204·8	11·8

As M stands for any molecule, an inert gas also accelerates the decomposition of the complex HOOBr, by which the reaction has been inhibited. In many experiments we have diluted the concentration of the reactants with nitrogen, thus increasing the total pressure. The results are summarised in Table III.

The experiments at 490°, 520°, 550°, 560°, and 605° led to the same result. The velocity constant depends in just the same way upon the total pressure, as the added neutral gas slackens the reaction according to equation (2).

The mean values of all experiments are summarised in the Table V.

Experiments at 635° did not give reproducible constants (see Table IV), especially with vessels that had undergone long heating at this temperature, and we attribute this to a change in the structure of the wall of the vessel. That this lack of constancy is not due to impurities in the gas follows from control experiments at 575°, which were satisfactory.

Homogeneity of the Reaction.—As a further test of the homogenity of the reaction, we increased the ratio of surface to volume about 70-fold by filling the vessel with capillary rings of the same glass, and although the constants were slightly different from those obtained before (being higher at low temperatures and *vice versa*), the deviation was of a smaller order of magnitude than the above ratio, and we deduce that the glass wall is only responsible for less than 5% of the total reaction.

Discussion.—It is first necessary to convert k from the units mm./min. to mols. l.$^{-1}$ sec.$^{-1}$, and the values of log k_c thus obtained are in line 2 of Table V. From the data at 833° and

TABLE V.

t° C.	490	520	550	560	575	605
T°, K.	763	793	823	833	848	878
$k_p\times10^3$, exp.	0·3878	1·39	2·028	2·308	3·003	7·941
log k_c, exp.	−0·979	−0·494	−0·228	−0·150	−0·045	0·353
log k_c, calc.	−1·034	−0·616	−0·236	−0·117	0·062	0·398

878° K., and with log $k_1 = 0·353$ and 0·150, respectively, we obtain the activation energy $Q = 37·3$ kcals. From this we determine the theoretical values of k_c by the formula

$$\log k_c = -Q/4{,}571T + \tfrac{1}{2}\log T + \log Z_0 + \log f \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where Z_0 is the collision number at 1° K. and f is the steric factor. For the calculation of Z from the formula

$$Z = 5·64 \times 10^{23}\, s_1 s_2 \sqrt{T}\,\sqrt{(M_1 + M_2)/M_1M_2}$$

we have M_1 (for HBr) = 82·294; M_2 (for O_2) = 32·000; s_1 (for HBr) = 3·06 A.; s_2 (for O_2) = 3·2 A.; whence we find log Z_0 = 10·061 mols. l.$^{-1}$ sec.$^{-1}$ at 1° K. Insertion of this

value into (3) with one value of k_c gives $\log f = -1{\cdot}826$ or $f = 0{\cdot}015$, a value often found in similar reactions. Substitution of this value in the equation giving k_c leads to the values in line 3 of Table V. The agreement between the experimental and the calculated values, coupled with the plausible values for Q and f, affords strong support for the mechanism outlined.

No information can be obtained as to the individual values of k_1' and k_2, their ratio having been found by trial and error. If k_1'/k_2 is made larger than 10 or smaller than 0·1, k_c becomes markedly dependent upon pressure. Moreover, the ratio 1 leads to an improbably small value of f, whereas if $k_1'/k_2 = 10$, $\log f = -1{\cdot}355$, the probable upper limit.

Hence, the oxidation of hydrogen bromide is a catalysed reaction type. The added inert gas inhibits the process. The inhibitory effect is manifested by the decomposition of the intermediate complex. The oxidation of hydrogen bromide is therefore, in our opinion, unique as a case of a negative catalysis through deactivation in a thermal reaction, no examples of this kind of catalysis having yet been reported (see Schwab, Taylor, and Spence, "Catalysis," New York, 1937).

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174. *Picrotoxinin and Tutin. Part III. The Hydrogenation of Picrotoxinin.*

By S. N. SLATER.

By treatment with bromine water of the reaction product obtained in the hydrogenation of picrotoxinin with palladium catalysts in the presence of acid, bromo*neo*picrotoxinin is formed which can be reduced to *neo*picrotoxinin, $C_{15}H_{16}O_6$, an isomeride of picrotoxinin. It is the hitherto postulated "picrotonol precursor," its acetyl derivative being identical with the acetyl derivative of the "picrotonol precursor." Dihydro*neo*picrotoxinin is identical with "β-dihydropicrotoxinin." The relationship between picrotoxinin and *neo*picrotoxinin is discussed. The lactone system of bromo*neo*picrotoxinin is unique in the picrotoxinin series in that it may be reversibly opened. The methylation of β-bromopicrotoxinic acid is described.

THE hydrogenation of picrotoxinin in the presence of palladium has been investigated by Mercer and Robertson (*J.*, 1936, 288) and by O'Donnell, Robertson, and Harland (*J.*, 1939, 1261), who have shown that the reaction is a complex one, leading (in neutral solution) to the formation of a mixture which on hydrolysis with 5% sulphuric acid yields β-dihydropicrotoxinin, dihydropicrotoxic acid, and picrotonol. The last two products are believed to arise from the action of the acid upon α-dihydropicrotoxinin and a "picrotonol precursor," respectively, and it is suggested that the picrotonol precursor may be an isomeride of picrotoxinin formed under the conditions of hydrogenation. The picrotonol precursor itself could not be isolated, but it was possible to obtain an acetyl derivative, presumably derived from it.

In Part I of this series (*J.*, 1943, 50) the author showed that tutin, $C_{15}H_{18}O_6$, the poisonous principle of the coriaria species of New Zealand, on hydrogenation in the presence of palladium and subsequent treatment with bromine water, gave a substance, believed at first to be a bromohydrotutin, $C_{15}H_{19}O_6Br$, but later (Part II, *ibid.*, p. 143) regarded as possessing the formula $C_{15}H_{17}O_6Br$. Similar results were obtained by hydrogenating picrotoxin and treating the product with bromine water, whereby a substance $C_{15}H_{15}O_6Br$ ("bromohydropicrotoxinin") was produced. It was suggested that these bromo-derivatives might have arisen from isomerisation products of tutin and picrotoxinin, formed under the influence of the catalyst and hydrogen. Attempts to repeat this work failed in the first instance.

A further investigation of the hydrogenation of picrotoxin and picrotoxinin in ethyl-alcoholic solution in the presence of a palladium–charcoal catalyst has provided an explanation of the discordant results and has led to the isolation of the previously postulated isomeride of picrotoxinin, the picrotonol precursor. If the hydrogenation is prolonged over several days the initial rapid uptake of hydrogen is succeeded by a slow absorption, considerably in excess of that required to saturate one double bond, and the final product does not react with bromine water. On the other hand, if the hydrogenation is stopped after the first rapid absorption of hydrogen is complete then the product (from either picrotoxin or picrotoxinin) reacts readily with bromine water to give the substance $C_{15}H_{15}O_6Br$, now named bromo*neo*picrotoxinin. This may be debrominated with zinc to yield an isomeride of picrotoxinin, $C_{15}H_{16}O_6$, for which the name neo*picrotoxinin* is suggested. It is a crystalline, optically active compound, similar

in its general behaviour to picrotoxinin. For instance, addition of bromine water to its hot aqueous solution precipitates bromo*neo*picrotoxinin, although only one modification is obtained in contrast to the α- and β-modifications of bromopicrotoxinin. On heating, it reduces both Fehling's solution and ammoniacal silver nitrate. It is soluble in alkali but is not reprecipitated on acidification. Its ultra-violet spectrum shows only end absorption.

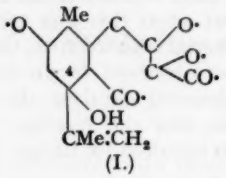
At this stage it appeared likely that *neo*picrotoxinin would prove identical with the picrotonol precursor, and confirmation of this view was found in its conversion into acetyl*neo*picrotoxinin, $C_{17}H_{18}O_7$, identical with a specimen of the acetyl derivative of the picrotonol precursor, prepared as described by O'Donnell, Robertson, and Harland (*loc. cit.*). That *neo*picrotoxinin was present in the particular specimen of crude hydrogenated picrotoxinin from which Robertson and his co-workers' acetate was prepared was shown by bromination of a portion of the material to give bromo*neo*picrotoxinin. The fact that β-dihydropicrotoxinin, like *neo*picrotoxinin, can be acetylated whilst picrotoxinin and α-dihydropicrotoxinin cannot, made it likely also that β-dihydropicrotoxinin was derived from *neo*picrotoxinin rather than picrotoxinin, and this was confirmed by hydrogenating *neo*picrotoxinin to *dihydroneopicrotoxinin*, $C_{15}H_{18}O_6$, which proved to be identical with a specimen of β-dihydropicrotoxinin prepared by the method of Robertson *et al.* In carrying out this hydrogenation it was considered desirable to use a platinum catalyst in acetic acid solution, since these conditions do not lead to secondary changes during the hydrogenation of picrotoxinin, but when this was attempted it was found that although hydrogen was absorbed the only pure material isolated from the reaction mixture was unchanged *neo*picrotoxinin. The same effect was observed in an attempt to hydrogenate acetyl*neo*picrotoxinin: by use of a palladium–charcoal catalyst the expected dihydro-derivative was obtained. The yield, however, is poor, and the reaction is clearly complex since the absorption of hydrogen is much in excess of that required for simple saturation of the double bond.

In the further study of the formation of *neo*picrotoxinin from picrotoxinin constant use was made of the characteristic formation of the readily recognisable bromo*neo*picrotoxinin, which simplified the otherwise difficult task of establishing the presence or absence of the isomeride in complex reaction mixtures. This isomerisation is dependent upon three factors: the use of palladium, the presence of hydrogen, and the presence of acid. The fact that no isomerisation occurs in the absence of hydrogen was observed by O'Donnell, Robertson, and Harland (*loc. cit.*) and this has been confirmed. This limits the yield of *neo*picrotoxinin, since hydrogenation invariably accompanies isomerisation. In an attempt to overcome this difficulty the reaction was carried out in an initially attenuated atmosphere of hydrogen, but without any improvement in the yield. The importance of the acid was shown by the use of neutral or slightly alkaline catalysts of proved activity in other hydrogenations or when used with picrotoxinin in acid solution. Thus, using palladium–barium sulphate, the absorption of hydrogen was negligible. With Raney nickel, a very slow absorption of hydrogen took place but the product on brominaton yielded only bromopicrotoxinin. Palladium–charcoal, as ordinarily prepared, is always acid in reaction unless special precautions are taken in the final stages. If such a catalyst is neutralised and used in the hydrogenation of picrotoxinin, the uptake of hydrogen is again slow and bromination of the product gives only bromopicrotoxinin. The residual acidity of palladium–charcoal catalysts is evidently sufficient, when working in otherwise "neutral" solutions (*e.g.*, hydrogenation in alcohol), to bring about the isomerisation.

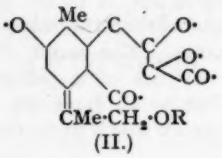
In considering the possible relationship between picrotoxinin and *neo*picrotoxinin the following five observations appear to be of importance: (*a*) The transformation takes place only in the presence of palladium, hydrogen, and acid. (*b*) Whereas picrotoxinin does not give an acetyl derivative, *neo*picrotoxinin can be acetylated, suggesting (O'Donnell, Robertson, and Harland, *loc. cit.*) a change in function of the hydroxyl group from tertiary to primary or secondary. (*c*) Whereas bromination of picrotoxinin leads to a mixture of two (stereo-?) isomeric monobromo-substitution products, bromination of *neo*picrotoxinin gives only one monobromo-substitution product. The rapid hydrogenation of picrotoxinin in acetic acid solution in the presence of a platinum catalyst may likewise be contrasted with the great resistance of *neo*picrotoxinin to hydrogenation under similar conditions. These two observations suggest a change in the molecular environment of the double bond. (*d*) As is shown below, bromo*neo*picrotoxinin differs strikingly from the bromopicrotoxinins in its behaviour with alkali, since the opening of the lactone system in this case is reversible. (*e*) When boiled with dilute mineral acid picrotoxinin gives the hydroaromatic picrotoxic acid but *neo*picrotoxinin gives the aromatic picrotonal.

Although the full significance of (*a*) is not yet apparent, (*b*) and (*c*) suggest some sort of allyl-

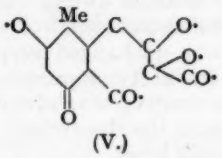
like rearrangement. Employing the partial formula for picrotoxinin developed by Harland and Robertson (*J.*, 1939, 937) and placing the tertiary hydroxyl group at C_4, the allyl position with respect to the double bond, the partial formula (I) is obtained which by allyl rearrangement would give (II; R = H) for *neo*picrotoxinin. Such further evidence as has been obtained, however, is mainly against this hypothesis: (i) It is not possible to dehydrate picrotoxinin to the corresponding diene, and it is conceivable that the molecular environment of the C_4 hydroxyl group of (I) might be such that a simple dehydration would be impossible. However, α-dihydropicrotoxinin (III on this formulation) should presumably undergo simple dehydration. It is, however, remarkably stable to acid dehydrating agents and was recovered unchanged after boiling with 85% formic acid, fused oxalic acid, or syrupy phosphoric acid. (ii) The oxidation of a structure such as (II; R = H) by the Oppenauer method, using acetone, would be expected to give (IV) (cf. Heilbron, Johnson, and Jones, *J.*, 1939, 1560) but *neo*picrotoxinin was recovered unchanged from such an experiment. (iii) The ozonolysis of *neo*picrotoxinin, formulated as (II; R = H), would be expected to give the ketone (V), and moreover, the same ketone should be obtained by ozonolysis of acetyl*neo*picrotoxinin (II; R = Ac, on this formulation). The study of this reaction is not yet completed, but the available evidence, particularly that bearing on the identity or otherwise of the two ozonolysis products, is against its taking this course.



(I.)

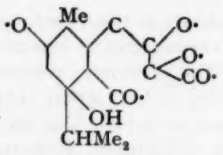


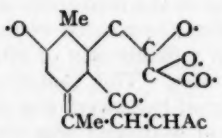
(II.)



(V.)

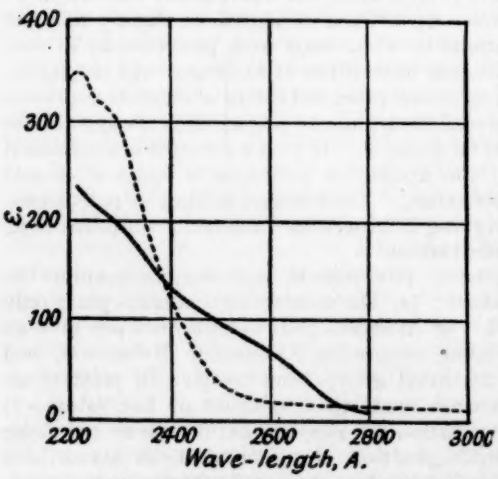
(III.)





(IV.)

Repeated ozonolysis of *neo*picrotoxinin, dissolved in ethyl acetate, gives in high yield a crystalline *substance*, $C_{12}H_{12}O_7$, m. p. 181—182°, whose molecular formula differs by the elements of water from that for (V). Unfortunately, this substance suffers some decomposition on prolonged heating even at moderate temperatures, and hence it was not possible to determine whether or not this loss is due to water of crystallisation, which is held tenaciously by many derivatives of picrotoxinin. The substance is neutral but devoid of carbonyl activity as shown by the non-formation of a 2 : 4-dinitrophenylhydrazone or semicarbazone, and the absence of any characteristic absorption in the ultra-violet absorption spectrum (see Fig.). It is a very strong reducing agent, reacting immediately in the cold with ammoniacal silver nitrate and alkaline potassium permanganate. This immediate reduction of alkaline permanganate appears to be a specific function of the newly generated functional grouping, since α-dihydropicrotoxinin and dihydro*neo*picrotoxinin do not show this reaction. With aqueous potassium hydroxide it reacts readily in the cold, giving a yellow solution turning red on warming and becoming colourless on acidification but without regeneration of the parent body. The same effect is observed if the substance is boiled with aqueous sodium hydrogen carbonate. It absorbs hydrogen under catalytic conditions (Adams's catalyst and acetic acid), although no pure substance has been isolated from the hydrogenation. The other product to be expected from the ozonolysis of (II; R = H) would be hydroxyacetone, and the behaviour of the



aqueous mother-liquor remaining from the decomposition of the ozonide of *neo*picrotoxinin was compatible with its presence. For instance, it gave a deep red colour with 40% aqueous potassium hydroxide, reduced ammoniacal silver nitrate in the cold immediately, and on distillation deposited a red resin and gave no detectable volatile carbonyl compound in the distillate. That the hydroxyl group has been lost on ozonolysis is indicated by the fact that the substance was recovered unchanged from an attempted acetylation (treatment with acetic anhydride and pyridine for two days at room temperature).

Ozonolysis of acetyl*neo*picrotoxinin also gives a second *substance*, $C_{12}H_{12}O_7$, m. p. 181—182°, but whereas the above compound from *neo*picrotoxinin is optically inactive, that obtained from acetyl*neo*picrotoxinin is optically active and the two show a mixed melting point depression. They also differ somewhat in their behaviour with aqueous potassium hydroxide, the compound from acetyl*neo*picrotoxinin showing little apparent reaction in the cold, and even on warming the crystals react only sluggishly, the solution becoming yellow.

It is evident from the published results (see especially Horrmann and Prillwitz, *Arch. Pharm.*, 1920, **258**, 200; Mercer and Robertson, *loc. cit.*; O'Donnell, Robertson, and Harland, *loc. cit.*) that the ozonolysis of picrotoxinin itself and its derivatives is by no means a simple reaction, and a further study of this is in progress. Preliminary experiments confirm the generation of formaldehyde, as described by Robertson and his co-workers, but the properties of the α-picrotoxinone formed at the same time, like those of the ozonolysis product of *neo*picrotoxinin, are somewhat anomalous. The analytical figures for the crystallised material which has been exhaustively dried agree with the required molecular formula $C_{14}H_{14}O_7$, but the ultra-violet absorption spectrum of the crude product (employed in preference to the crystallised material in order to eliminate the possibility of contamination with the β-modification; Horrmann and Prillwitz, *loc. cit.*) does not indicate the presence of a carbonyl group (see Fig.), and the characteristic semicarbazone, described by Horrmann and Prillwitz (*loc. cit.*), could not be prepared.

Like bromopicrotoxinin, bromo*neo*picrotoxinin reacts on warming with dilute sodium hydroxide solution, but while the former reaction is facile and irreversible by acidification, the latter is much slower and reversible, the corresponding free hydroxy-acid passing back very readily into the parent lactone. This appears to be the only example yet described of a member of the picrotoxinin series in which a lactone system can be reversibly opened. The crude bromo*neo*picrotoxinic acid can be readily obtained by precipitation of a cold aqueous solution of the sodium salt with mineral acid, but its crystallisation is difficult and on only one occasion was a satisfactory sample obtained; it then crystallised on standing in the ice-chest from a dilute acidified solution of the sodium salt. The analytical figures agree with $C_{15}H_{19}O_8Br$, which is regarded as the *hydrate* of *bromoneopicrotoxinic acid*, $C_{15}H_{17}O_7Br,H_2O$, the monocarboxylic acid corresponding to the α- and the β-bromopicrotoxinic acid, which retain water of crystallisation most tenaciously. The reversible nature of this reaction is considered to be of some importance. Its further study should be facilitated by stabilisation of the hydroxy-acid as the methyl ether. This methylation process has been little studied in the picrotoxin series, although Mercer and Robertson (*loc. cit.*) have described the conversion of dihydropicrotoxic acid into its dimethyl ether by the silver oxide method. There are obvious analogies between picrotoxinin, with its highly oxygenated side chain, and the sugars, and it seems likely that the investigation of its methylated derivatives will yield important results. The stability to alkali of the various brominated acids in this series suggested that the methyl sulphate method might be applicable, and a preliminary series of experiments has confirmed this in the case of β-bromopicrotoxinic acid, which can be converted into O-*methyl* β-*bromopicrotoxinic acid*.

Experimental.

Palladium Catalyst.—Palladous chloride (0·2 g.), dissolved in concentrated hydrochloric acid (0·5 c.c.) and then diluted with water, was added to norit (2 g.) which had been heated to 140° in an evaporating dish with constant stirring, cooled in a vacuum desiccator, and mixed with water (100 c.c.). The catalyst mixture was reduced with hydrogen, and the palladium–charcoal catalyst then filtered off, washed with distilled water, absolute alcohol, and finally absolute ether, after which it was transferred to a vacuum desiccator.

Hydrogenation and Bromination Experiments.—(*a*) The following method gave reproducible yields of bromo*neo*picrotoxinin: Picrotoxin (2·0 g.), dissolved in alcohol, was shaken with the palladium–charcoal catalyst (0·4 g.) at atmospheric pressure in the presence of hydrogen. When the first relatively rapid absorption of hydrogen had ceased (usually about 35—40 c.c. during 15—120 minutes, depending on the activity of the particular sample of catalyst), the hydrogenation was interrupted, the catalyst filtered off, and the alcoholic solution evaporated in a vacuum on the water-bath. The residue, frequently obtained as a viscous gum, was dissolved by boiling with water (during this process any viscous material solidified to hard white granules which were ground to facilitate solution) and an excess of bromine water was then

added. After stirring and standing for a short while the reaction mixture deposited a white precipitate which was filtered off, washed with water, and dried; yield, 0·4 g. of clean but unpurified material. The delayed precipitation of bromo*neo*picrotoxinin is in sharp contrast to the immediate precipitation of bromopicrotoxinin under similar conditions. Crystallisation from alcohol (best by the use of a thimble placed in the hot vapours of a reflux condenser, as the solubility in alcohol is quite low) gave glistening needles of the compound previously described as "bromohydropicrotoxinin." The m. p. of this substance is dependent upon the conditions under which it is observed. The value previously quoted (254—255°, decomp., with previous shrinking) is obtained by heating in the usual way. If the bath is pre-heated to just a few degrees below the m. p., however, a much sharper and considerably higher m. p. can be observed, *viz.*, 265° (decomp.). In the sections which follow, m. p.s within this region have been obtained from a bath pre-heated to *ca.* 260°, and lower figures have been obtained from a bath pre-heated to 230—240°. The above product showed no depression in m. p. when mixed with a specimen of "bromohydropicrotoxinin."

(*b*) Picrotoxinin, treated as above, yielded the same bromo-derivative, m. p. (twice recrystallised) 262—263°.

(*c*) Palladous chloride (0·06 g.), dissolved in dilute hydrochloric acid (1 drop of concentrated hydrochloric acid + 4 c.c. of water), was added to a solution of picrotoxin (2·0 g.) in glacial acetic acid (25 c.c.). After hydrogenation for 50 minutes (uptake of hydrogen *ca.* 40 c.c.) the catalyst and solvent were removed and the residue was brominated; yield, 0·3 g. The product, crystallised from alcohol, had m. p. 253° (decomp.). There was no mixed m. p. depression with bromo*neo*picrotoxinin.

(*d*) When picrotoxinin in alcohol was shaken with the palladium–charcoal catalyst it was found, in agreement with the results of O'Donnell, Robertson, and Harland (*loc. cit.*), that no change occurred, the recovered material showing no mixed m. p. depression with the starting material.

(*e*) A specimen of a particularly active palladium–charcoal catalyst was shaken for several hours with aqueous alkali in the presence of hydrogen, filtered off, and washed repeatedly with hot water until the washings were only very slightly alkaline to phenolphthalein. By means of this neutralised catalyst, picrotoxinin (1·0 g.) was hydrogenated for 80 minutes (hydrogen uptake 32 c.c.), whereupon the experiment was stopped although slow absorption was still taking place. On bromination the product gave a bromo-derivative (0·6 g.), m. p. (after two crystallisations from alcohol) 268° (decomp.), which showed a strong mixed m.p. depression with bromo*neo*picrotoxinin but no depression with a sample of β-bromopicrotoxinin of approximately the same degree of purity.

(*f*) When a catalyst was used which had been made definitely alkaline to phenolphthalein, the absorption of hydrogen was negligible. After some time the hydrogenation was interrupted, a few drops of concentrated hydrochloric acid added, and shaking with hydrogen recommenced. Very little additional absorption took place, but the product on bromination yielded bromo*neo*picrotoxinin, m. p. 251° (decomp.) and showing no depression with authentic material.

(*g*) When picrotoxinin (1·0 g.) in alcohol was hydrogenated in the presence of Raney nickel catalyst, a very slow absorption took place (20 c.c. after 1½ hours' shaking and then standing overnight) but the product on bromination yielded only bromopicrotoxinin.

neo*Picrotoxinin*.—Bromo*neo*picrotoxinin (0·4 g.) in boiling alcohol (8 c.c.) was treated with a solution of ammonium chloride (0·08 g.) in water (0·4 c.c.), followed by zinc dust (0·12 g.) added in small quantities. Further additions of similar amounts of ammonium chloride solution and zinc dust were made, the volume of the reaction mixture being kept approximately constant by the addition of alcohol as required. After 20 minutes' boiling the product was clarified (norit) and filtered, giving a clear pale yellow solution which was evaporated to dryness. The residue was washed with a small quantity of 2N-sulphuric acid, then with cold water, and finally boiled with two successive portions of water to complete solution. Of the two crops of crystals obtained from these two extracts (0·05 g. and 0·06 g., respectively) the second was the cleaner and was further purified and examined. On recrystallisation it was obtained as fine white soft needles (0·04 g.), m. p. (bath pre-heated to 190°) *ca.* 204° after much softening, mixed m. p. with picrotoxinin, *ca.* 185° (Found, after drying in a vacuum desiccator overnight: C, 59·6; H, 6·0. $C_{15}H_{16}O_6,\frac{1}{2}H_2O$ requires C, 59·8; H, 5·65%). This neo*picrotoxinin hemihydrate* was again crystallised from water and then dried in a vacuum at 110° for several hours, giving the anhydrous neo*picrotoxinin*, m. p. *ca.* 212° (decomp.) after much previous softening (Found: C, 61·6; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%). In subsequent preparations it was found that the yield varies with the period of heating of the bromo-derivative with the zinc, the highest yields (1·0—1·3 g. from 2·0 g. of bromo-derivative) being obtained by a short period. Under these conditions, also, the m. p. was somewhat higher (*ca.* 220°, decomp.) although still indefinite with much previous softening (Found: C, 61·4, 61·3; H, 5·5, 5·6%); $[\alpha]_D^{15\cdot5°}$ −18·8°.

Bromination of neo*Picrotoxinin*.—When bromine water was added to a hot aqueous solution of *neo*picrotoxinin, a white precipitate formed on standing which on recrystallisation (twice) from alcohol melted at 254° (decomp.) and showed no depression with a specimen of bromo*neo*picrotoxinin, m. p. 256° (decomp.).

*Acetyl*neo*picrotoxinin*.—(*a*) *Indirect preparation from picrotoxinin* (O'Donnell, Robertson, and Harland, *loc. cit.*). Picrotoxinin (1·0 g.) was hydrogenated either in alcohol by use of a palladium–charcoal catalyst or in acetic acid with palladous chloride. A portion of the product was brominated, yielding bromo*neo*picrotoxinin, m. p. 257° (decomp.) undepressed by admixture with authentic material. The remainder (0·5 g.) was acetylated as described by Robertson *et al.* and crystallised from alcohol; yield, 0·2 g., m. p. 188°, raised by two further crystallisations to 190—190·5°.

(*b*) *Direct preparation from* neo*picrotoxinin*. *neo*Picrotoxinin (0·5 g.) was acetylated in the same way, giving a crude product (0·5 g.), m. p. *ca.* 180°, raised after three crystallisations from alcohol to 189—189·5° and showing no mixed m. p. depression with the above specimen (Found: C, 60·8; H, 5·5. Calc. for $C_{17}H_{18}O_7$: C, 61·1; H, 5·4%).

*Dihydro*neo*picrotoxinin*.—(*a*) *Indirect preparation from picrotoxinin* (Mercer and Robertson, *J.*, 1936, 288; O'Donnell, Robertson, and Harland, *loc. cit.*). Picrotoxinin (2·0 g.) in alcohol (100 c.c.) was hydrogenated in the presence of charcoal (1·0 g.) and palladous chloride (0·1 g.) in water (10 c.c.). After

6 hours the product was filtered, evaporated to small bulk, and diluted with water. The material which crystallised out on standing (1·1 g.) was heated under reflux for 12 hours with 1·5N-sulphuric acid (20 c.c.). After standing overnight, the " β-dihydropicrotoxinin " which was precipitated was crystallised from alcohol (charcoal); m. p. 255—256°.

(*b*) *Direct preparation from* neo*picrotoxinin.* *neo*Picrotoxinin (0·1 g.) in alcohol was hydrogenated overnight in the presence of an active palladium–charcoal catalyst, the uptake of hydrogen being *ca.* 100 c.c. The product, on crystallisation from aqueous alcohol, gave a small yield of *dihydroneopicrotoxinin*, m. p. 255—256° undepressed on admixture with the above " β-dihydropicrotoxinin " (Found: C, 61·1; H, 6·5. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%).

Ozonolysis of neo*Picrotoxinin.*—*neo*Picrotoxinin (1 g.) in absolute ethyl acetate (25 c.c.) was ozonised for 2 hours, the solvent distilled off in a vacuum at 30°, and the residual crystalline ozonide decomposed by standing overnight with water. The product was filtered off and crystallised from methanol and then ethanol; m. p. 181° (decomp.). The same product, m. p. and mixed m. p. 181°, was obtained when the period of ozonolysis was prolonged to 20 hours (Found: C, 54·5, 54·2; H, 4·7, 4·5%). This product gave a red colour in the cold with concentrated aqueous potassium hydroxide. When a sample of this once-ozonised *neo*picrotoxinin was dissolved in ethyl acetate and again ozonised for 2 hours, decomposed with water, and crystallised from ethanol, the resulting *product* had a slightly higher m. p. (182°, decomp., showing no depression when mixed with the starting material) and gave a yellow colour in the cold with concentrated aqueous potassium hydroxide, the red colour appearing only on heating. The analytical figures were also appreciably different (Found: C, 53·7, 53·9; H, 4·7, 4·5. $C_{15}H_{18}O_7$ requires C, 53·7; H, 4·5%).

*Ozonolysis of Acetyl*neo*picrotoxinin.*—Acetyl*neo*picrotoxinin (200 mg.) in ethyl acetate was ozonised and worked up as above; m. p. 181—182° (Found: C, 53·5; H, 4·8. $C_{15}H_{12}O_7$ requires C, 53·7; H, 4·5%); $[\alpha]_D^{12°}$ + 56°. A mixed m. p. depression was observed both with the starting material and with the above ozonolysis product of *neo*picrotoxinin. The aqueous mother-liquors remaining from the decomposition of the ozonide reduced ammoniacal silver nitrate only an heating, and with concentrated aqueous potassium hydroxide gave no colour in the cold but developed a yellow colour on heating.

Ozonolysis of Picrotoxinin.—Picrotoxinin (5 g.) in ethyl acetate (200 c.c.) was ozonised until a specimen of the reaction mixture after evaporation and solution in boiling water no longer gave a precipitate with bromine water (*ca.* 18 hours). After the solvent had been removed in a vacuum at 30° the residual solid ozonide was treated with water, broken up with a stirring rod, and set aside overnight. It was then filtered off, and a specimen crystallised from aqueous alcohol. Without special drying the crystals thus obtained shrank immediately when placed in a melting-point bath at 110°. The m. p. was quite indefinite. The product was therefore dried for a prolonged period in a vacuum over phosphoric oxide, first at room temperature and finally at a temperature which was gradually increased to 90°. The m. p., from a bath preheated to 160°, was now *ca.* 180° after much previous softening (Found: C, 56·7; H, 4·6. Calc. for $C_{14}H_{14}O_7$: C, 57·2; H, 4·8%). The aqueous mother-liquors remaining from the decomposition of the ozonide were distilled to small bulk and the distillate treated with an excess of aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. The resulting yellow precipitate was collected and crystallised from alcohol; m. p. 163° undepressed with authentic formaldehyde 2 : 4-dinitrophenylhydrazone.

Reaction of Bromoneopicrotoxinin with Alkali.—Bromo*neo*picrotoxinin (0·1 g.) was warmed to solution with 2N-sodium hydroxide and then acidified with dilute mineral acid. On standing in the ice-chest, *bromoneopicrotoxinic acid* crystallised out in beautiful needles (0·06 g.), m. p. 225—226° (decomp.) from a bath preheated to 220° (Found: C, 44·3; H, 4·9; Br, 18·7,* 21·5.* $C_{15}H_{19}O_8Br$ requires C, 44·2; H, 4·7; Br, 19·7%). In a further preparation, bromo*neo*picrotoxinin (0·5 g.) was dissolved by boiling with dilute aqueous sodium hydroxide, and the cold solution was acidified with a little concentrated hydrochloric acid. The crude precipitated material (0·42 g.) was taken up in sodium hydrogen carbonate solution and reprecipitated with acid. The m. p., taken in the usual way, was *ca.* 217° after very noticeable shrinking and blackening at lower temperatures, but when placed in a pre-heated bath it melted immediately. By trial, the true m. p. (clean decomposition without blackening) appears to be 195—196° from a bath pre-heated to 193°. In one of several attempts to recrystallise the acid, it was dissolved in chloroform, some light petroleum (b. p. 60—80°) added, and the resulting slightly cloudy solution dried (Na_2SO_4) and filtered. On slow evaporation at room temperature well-formed crystals were left, but satisfactory analytical figures were not obtained, much solvent of crystallisation being retained. When the crude acid was crystallised from dilute acetic acid, well-formed crystals were obtained, m. p. 245° (decomp.) unchanged by recrystallisation from glacial acetic acid and showing no mixed m. p. depression with bromo*neo*picrotoxinin (Found: C, 48·2; H, 4·2. Calc. for $C_{15}H_{15}O_6Br$: C, 48·5; H, 4·0%). The re-formation of the lactone from the acid was frequently observed in the course of its examination.

O-*Methyl β-Bromopicrotoxinic Acid.*—β-Bromopicrotoxinic acid (0·5 g.) was treated dropwise with methyl sulphate (0·5 g.) and 40% aqueous potassium hydroxide so that the reaction mixture was always slightly alkaline. On acidification, the hot solution rapidly precipitated an *acid*, which was filtered off, dried (yield, 0·3 g.), and crystallised from water and then alcohol; m. p. 244° (decomp.) (Found: C, 46·8; H, 4·5; Br, 20·3*; OMe, 7·7.* $C_{16}H_{19}O_7Br$ requires C, 47·7; H, 4·7; Br, 19·8; OMe, 7·7%). A strong mixed m. p. depression was observed with the starting material.

The author's thanks are due to Messrs. T. & H. Smith, Edinburgh, for a gift of picrotoxin, to Mr. C. L. Carter, M.Sc., for performing certain of the micro-analyses, to Mr. F. C. Baker for polarimetric determinations, and to Mr. S. J. Woodcock for ultra-violet spectra determinations. Grateful acknowledgment is made of the generous hospitality of Professor A. R. Todd, F.R.S., and the Chemical Laboratories, Cambridge, extended to the author while on leave of absence.

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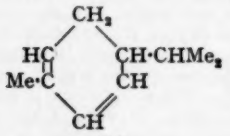
* Analyses by Drs. Weiler and Strauss, Oxford.

175. *Application of the Diene Synthesis to Terpenoid Compounds. Part III. Reaction between β-Phellandrene and β-Naphthol.*

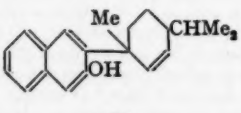
By G. G. Acheson and T. F. West.

The addition product formed between (−)-β-phellandrene and β-naphthol is shown to be identical with that obtained from (−)-α-phellandrene (cf. Salfeld, *Ber.*, 1940, **73**, 376). During the reaction more than 50% of the (−)-β-phellandrene is converted into (−)-limonene. It would appear that an unstable intermediate compound may be formed which then decomposes to give the (−)-α-phellandrene adduct and (−)-limonene, but attempts to isolate such an initial product were unsuccessful.

Salfeld (*Ber.*, 1940, **73**, 376) has pointed out that reactions such as the conversion of β-naphthol into β-naphthylamine on treatment with sodium hydrogen sulphite and ammonia are usually explained by postulating an intermediate carbonyl form for the phenol and that such a structure might be expected to behave as a dienophile in the Diels–Alder reaction. On heating β-naphthol with α-phellandrene (I) at 130° for 15 hours, Salfeld did obtain a product containing the reactants in the proportion 1 : 1, but from a consideration of the properties of this adduct he decided that addition had not taken place in a 1 : 4 position to the conjugated system of the terpene and assigned the formulæ (II) and (III) respectively to this compound and to the *iso*-adduct into which it was converted readily on treatment with (among other reagents) a methyl-alcoholic solution of hydrochloric acid. The *iso*-adduct was also obtained directly from β-naphthol and α-phellandrene when the condensation was effected under the conditions specified by Claisen (*Ber.*, 1921, **54**, 200; cf. Smith *et al.*, *J. Org. Chem.*, 1939, **4**, 311) which involve the use of an acid catalyst.



(I.)



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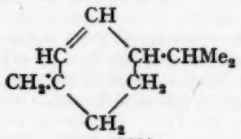

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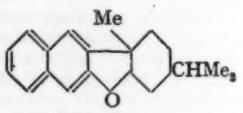


(III.)

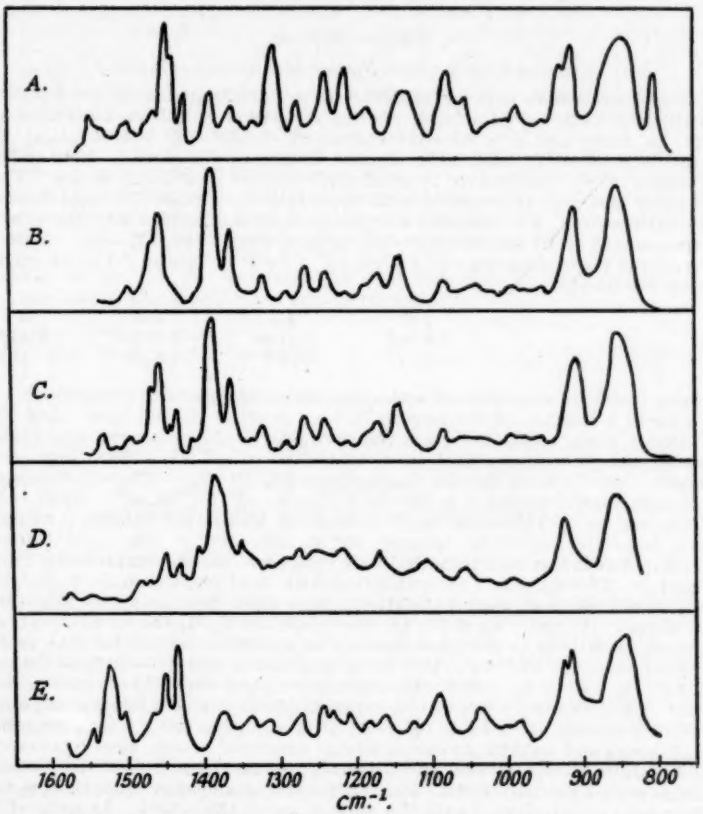
Salfeld reported that, when heated at 275° in the presence of selenium, the adduct was converted partly into its components, α-phellandrene and β-naphthol, but the method of identifying the terpene was not recorded. We have found that on distillation at atmospheric pressure, the adduct is decomposed into β-naphthol and α-terpinene.

In view of the behaviour of β-phellandrene (IV) towards maleic anhydride (Goodway and West, *J.*, 1938, 2028) and recent observations on the co-existence of α- and β-phellandrene in essential oils (*inter alii*, Berry, Macbeth, and Swanson, *J.*, 1937, 1443; Berry and Macbeth, *J.*, 1947, 1039), it appeared of considerable interest to investigate the reaction of this terpene with β-naphthol. (−)-β-Phellandrene can be obtained in a state of high purity from the readily available Canada balsam oil (Macbeth, Smith, and West, *J.*, 1938, 119). The adduct obtained from the (−)-β-phellandrene had m. p. 139—140° after recrystallisation from light petroleum, and $[\alpha]_D$ +124·8° (in alcohol). Now Salfeld recorded a m. p. of 139—140° for the adduct which he obtained from α-phellandrene but unfortunately neither the constants nor the source of his sample of terpene was specified. Accordingly, we prepared a sample of (−)-α-phellandrene by fractional distillation from the terpene fraction of the oil of *Eucalyptus dives* which had previously been rendered free from cineole. The adduct which we obtained therefrom had m. p. 138·5—139·5°, $[\alpha]_D$ +123·9° (in alcohol), and the melting point was not depressed on admixture with the adduct derived from the (−)-β-phellandrene (Acheson and West, *Nature*, 1948, **161**, 976). The identity of the adducts from the two terpenes was confirmed by preparing the *p*-nitrobenzoates and the *iso*-adducts. The infra-red absorption spectrograms of α- and β-phellandrene are distinct and characteristic (see figure) and, by this means, it was possible to detect as little as 5% of the α- in the presence of the β-isomeride in artificial mixtures of the two terpenes. This observation confirmed the conclusion reached by Goodway and West (*loc. cit.*; *J. Soc. Chem. Ind.*, 1937, **56**, 472T; 1938, **57**, 37) on chemical grounds that the (−)-β-phellandrene present in Canada balsam oil is free from the α-isomeride.

The yields of crude adduct from the α- and β-phellandrene were comparable (20—30% of the theoretical) and a method of purifying the adduct was devised so that the bulk of the unreacted terpene was recovered. After reaction of β-phellandrene with β-naphthol it was noticed that the terpene recovered failed to react with β-naphthol to give a further yield of adduct. It was

then observed that the constants had altered markedly and the flat nature of the ultra-violet absorption curve confirmed that β-phellandrene was not present (Booker, Evans, and Gillam, *J.*, 1940, 1453). This terpene was identified by the preparation of a tetrabromide of which the melting point was not depressed on admixture with a sample of authentic (−)-limonene tetrabromide. Furthermore, the infra-red absorption spectrogram of the recovered terpene was identical with that of dipentene (see figure).

Infra-red absorption spectrograms of terpenes.



Curve A—α-Phellandrene.
Curve B—β-Phellandrene.
Curve C—Recovered terpene from β-phellandrene–β-naphthol reaction.
Curve D—Dipentene.
Curve E—Recovered terpene from α-phellandrene–β-naphthol reaction.

The sample of (−)-α-phellandrene utilised in the reaction appeared, from its physical constants, to be in a fairly high state of purity although it was probably considerably less pure than the samples of the β-isomeride derived from Canada balsam oil. After reaction with β-naphthol the failure of the recovered terpene to react with maleic anhydride under mild conditions (Goodway and West, *J. Soc. Chem. Ind.*, 1937, **56**, 472T; Birch, *J. Proc. Roy. Soc. N.S.W.*, 1937, **71**, 261) and the nature of the ultra-violet absorption curve (Booker *et al.*, *loc. cit.*) proved that a conjugated system was no longer present, so the α-phellandrene had likewise undergone a reaction leading to redistribution of the double bonds. It has not proved possible to obtain crystalline derivatives from this product (probably a mixture owing to impurities in the original α-phellandrene) which remains unidentified, but the infra-red absorption spectrogram indicated that it did not contain limonene (see figure).

The β-phellandrene adduct (= α-adduct) was not decomposed into a terpene when heated at 147° for 15 hours; the oily by-product obtained on washing the crude β-phellandrene adduct with light petroleum was also unaffected by this treatment; the small amount of alkali-soluble material, isolated by acidifying the alkaline washes used to free the reaction product from

β-naphthol and extracting them with light petroleum, was not converted into a terpene on heating at 130° for 15 hours. Thus these three reaction products do not appear to be precursors of the (−)-limonene. (−)-β-Phellandrene was recovered unchanged when steam-distilled in the presence of β-naphthol, and when (−)-β-phellandrene was treated with ½ mol. of β-naphthol the terpene recovered consisted of a mixture of (−)-limonene and unreacted β-phellandrene. The latter observation and the persistence of optical activity suggest that an unstable intermediate is formed which decomposes to give (−)-limonene and the adduct as products. Unfortunately it has not proved possible to isolate such an intermediate compound.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Reaction of (−)-β-Phellandrene with β-Naphthol.—In a typical experiment the β-phellandrene derived, by fractional distillation using a Podbielniak column, from Canada balsam oil (Smith and West, *J. Soc. Chem. Ind.*, 1937, **56**, 300T) had b. p. 42—43°/4 mm., $n_D^{20°}$ 1·4805, $\alpha_D^{25°}$ −43·4°, $\lambda_{max.}$ 2320 A., $\varepsilon_{max.}$ 8300 (cf. Macbeth, Smith and West, *J.*, 1938, 119; Booker, Evans, and Gillam, *J.*, 1940, 1453). This terpene (40 g.) and β-naphthol (80 g.) were heated in an oil-bath at 128° ± 2° for 20 hours. The cooled mixture was dissolved in ether (200 ml.) and washed with 2N-sodium hydroxide (300 ml.) three times, then with brine and finally with water. The ethereal solution was steam-distilled and the solution of recovered terpene in ether separated from the distillate (cf. Salfeld, *Ber.*, 1940, **73**, 382). Removal of the ether gave 22·6 g. of recovered terpene having $n_D^{20°}$ 1·4752, $\alpha_D^{25°}$ −74·2°. This oil (17 g.) on fractional distillation gave the following fractions:

Wt. (g.)	2·6	3·5	4·3	5·2	0·5
$n_D^{20°}$	1·4744	1·4746	1·4750	1·4754	Residue
$[\alpha]_D$ (in EtOH)	−71·9°	−77·7°	−81·5°	−88·8°	—

Portions of these fractions were treated with reagents in the following proportions. Bromine (1·1 g.) was added dropwise to a solution of the terpene (0·5 g.) in ethyl alcohol (2 ml.) and ether (1 ml.), kept at 0° to −5°. Under these conditions each fraction gave a crystalline tetrabromide (m. p. approx. 88—91°). A mixed sample recrystallised from ether had m. p. 103—104°, $[\alpha]_D^{20°}$ −65·4° (*c*, 1·07 in chloroform) (Found: Br, 70·7. Calc. for $C_{10}H_{16}Br_4$: Br, 70·2%). {Oil of *Abies alba* on fractional distillation gave (−)-limonene having b. p. 53—53·5°/7 mm., $n_D^{20°}$ 1·4726, $\alpha_D^{25°}$ −93·6°. The tetrabromide prepared therefrom had m. p. 103—104°, $[\alpha]_D^{20°}$ −72·8° (*c*, 1·03 in chloroform); mixed with the tetrabromide prepared from the recovered terpene, m. p. 103—104°.} The light brown, waxy residue remaining after steam-distillation was extracted with ether, and the ethereal solution boiled with charcoal to give a crude adduct (23·9 g.) which on trituration with light petroleum (b. p. 30—60°) gave 19·3 g., m. p. 128—134°, raised by five recrystallisations from light petroleum to 139—140°, $[\alpha]_D^{28°}$ 124·8° (*c*, 2,973 in ethyl alcohol) (Found: C, 85·7; H, 8·8. Calc. for $C_{20}H_{24}O$: C, 85·7; H, 8·6%). In other experiments (working essentially as described above or according to Salfeld, *loc. cit.*), using β-phellandrene having $n_D^{20°}$ 1·4796—1·4810, α_D −43° to −46°, the terpene recovered (56—70% of the weight taken) had $n_D^{20°}$ 1·4734—1·4755, $[\alpha]_D$ −61·4° to −82·6° (in ethyl alcohol) and the yield of crude adduct was 20—31% of the theoretical. The following is typical of experiments to utilise a neutral solvent in the reaction. β-Phellandrene (10 g.) having $n_D^{20°}$ 1·4803, $\alpha_D^{24°}$ −41·2°, β-naphthol (20 g.), and benzene (30 g.), heated under reflux for 15 hours and worked up essentially as described above, gave recovered terpene (5·8 g.) having b. p. 56—58°/12 mm., $n_D^{20°}$ 1·4795, $\alpha_D^{25°}$ −47·75°, and an oily adduct (2·1 g.) which on trituration with light petroleum gave a product (0·8 g.) which after recrystallisation from light petroleum had m. p. 136—137° not depressed on admixture with the adduct, m. p. 139—140°. In spite of the higher reflux temperatures, the yields of adduct were not increased when the reaction was carried out in toluene or xylene solution. Two other typical experiments were conducted as follows: (*a*) (−)-β-Phellandrene (20 g.) having $n_D^{20°}$ 1·4810, $\alpha_D^{22°}$ −43·8°, and β-naphthol (10·6 g.), heated at 130° for 15 hours, gave a crude adduct (6·5 g.) which was recrystallised to m. p. 139—140°. The recovered terpene (12·5 g.) had b. p. 72—74°/21 mm., $n_D^{20°}$ 1·4780, $\alpha_D^{24°}$ −58·4°, displayed a strong nitrosite reaction for phellandrene, and gave, in low yield, (−)-limonene tetrabromide, m. p. 101—102° after recrystallisation from ether, not depressed on admixture with authentic (−)-limonene tetrabromide. The sodium hydroxide washings on acidification gave 7·6 g. of product, m. p. 119—120° not depressed on admixture with β-naphthol. (*b*) (−)-β-Phellandrene (20 g.), treated as above with β-naphthol (21·2 g.), gave 9·9 g. of crude adduct which after two recrystallisations had m. p. 139—140°, and recovered terpene (14·1 g.) having b. p. 68—69°/15 mm., $n_D^{20°}$ 1·4751, $\alpha_D^{25°}$ −69·65°, from which (−)-limonene tetrabromide, m. p. (and mixed m. p.) 103—104°, was prepared.

A sample of recovered terpene (8·5 g.), having b. p. 77—78°/30 mm., $n_D^{20°}$ 1·4750, $[\alpha]_D^{20°}$ −85·8° (*c*, 1·05 in ethyl alcohol) (Found: C, 88·0; H, 11·6. Calc. for $C_{10}H_{16}$: C, 88·2; H, 11·8%), and β-naphthol (17 g.) were heated in an oil-bath at 130° for 15 hours, and the reaction mixture treated as before. The recovered terpene (7·1 g.) had b. p. 75—77°/30 mm., $n_D^{20°}$ 1·4750, $[\alpha]_D^{23°}$ −74·9° (*c*, 1·15 in ethyl alcohol), and only 0·96 g. of dark, oily adduct was obtained, which deposited a small amount of solid material on standing. After twice recrystallising from light petroleum, this product (30 mg.) had m. p. 135—137°, and mixed with β-phellandrene adduct, m. p. 135—138·5°.

Derivatives of the β-Naphthol Adduct Derived from β-Phellandrene.—By proceeding essentially as described by Salfeld (*loc. cit.*), the following were prepared: *iso*-adduct, m. p. 105—106° (Found: C, 86·0; H, 8·8. Calc. for $C_{20}H_{24}O$: C, 85·7; H, 8·6%); *p*-nitrobenzoate of the adduct, m. p. 164·5—165·5° (Found: C, 74·9; H, 6·4. Calc. for $C_{27}H_{27}O_4N$: C, 75·5; H, 6·3%).

Preparation of the Adduct from (−)-α-Phellandrene.—In a typical experiment (−)-α-phellandrene, prepared by fractional distillation from a terpene fraction of the oil of *E. dives*, previously rendered free

from cineole by repeated shaking with a 50% aqueous solution of resorcinol, had b. p. 49·5—50°/10 mm., $n_D^{20°}$ 1·4735, $\alpha_D^{25°}$ −102·5°, $\lambda_{max.}$ 2640 A., $\varepsilon_{max.}$ 2260 (cf. Booker *et al.*, *loc. cit.*). This sample (40 g.) and β-naphthol (80 g.) were heated together during 15 hours at 130°, and the product worked up as described above. The crude adduct (23·1 g.), m. p. 128—133°, on trituration with light petroleum, gave 14·9 g., m. p. 133·5—134°, raised by two recrystallisations to 138·5—139·5°, $[\alpha]_D^{26°}$ 123·9° (*c*, 4·947 in ethyl alcohol). The terpene recovered (20·8 g.) during the steam-distillation had b. p. 58—58·5°/13 mm., $n_D^{20°}$ 1·4775, $\alpha_D^{25°}$ −32·6°. The *iso*-adduct and the *p*-nitrobenzoate of the adduct (Salfeld, *loc. cit.*) had m. p. 106° and m. p. 164·5—165°, respectively. This adduct and these derivatives did not depress the m. p.s when admixed with the corresponding compounds derived from (−)-β-phellandrene.

Thermal Decomposition of the Adduct.—The adduct (8 g.) was distilled at atmospheric pressure with decomposition. The distillate was dissolved in ether, and washed three times with 2N-sodium hydroxide solution (40 ml.), with brine, and finally with water. The etheral solution on steam-distillation gave a terpene (1·7 g.), b. p. 68—69°/22 mm., $n_D^{20°}$ 1·4779, $\alpha_D^{24°}$ 5·0°, $\lambda_{max.}$ 2650 A., $\varepsilon_{max.}$ 2320. The infra-red absorption spectrogram corresponded with that of an authentic sample of α-terpinene, and the presence of this terpene was confirmed by the preparation (Gascoigne, *J. Proc. Roy. Soc. N.S.W.*, 1941, **74**, 353), in low yield, of the adduct with *p*-benzoquinone, m. p. 86—87°, not depressed on admixture with a sample, m. p. 86—87°, prepared from authentic α-terpinene having b. p. 52·5—53°/12 mm., $n_D^{20°}$ 1·4782, α_D^{25} ± 0°, $\lambda_{max.}$ 2655 A., $\varepsilon_{max.}$ 5000 (cf. Booker *et al.*, *loc. cit.*). On acidification the alkaline washings gave a product (1·9 g.), m. p. 120—121°, not depressed on admixture with β-naphthol.

Determinations of absorption spectra in the ultra-violet were made in alcoholic solution by means of a Beckman quartz spectrometer, and in the infra-red on the undiluted substances using a Perkin–Elmer infra-red spectrometer (Model 12B); standard procedures were employed.

We are indebted to Dr. D. H. Sheffield and the Hercules Powder Company for the gift of the terpinolene from which the α-terpinene was prepared.

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176. *Studies on Phosphorylation. Part V. The Reaction of Tertiary Bases with Esters of Phosphorous, Phosphoric, and Pyrophosphoric Acids. A New Method of Selective Debenzylation.*

By J. BADDILEY, V. M. CLARK, J. J. MICHALSKI, and A. R. TODD.

Neutral benzyl esters of phosphorous, phosphoric, and pyrophosphoric acids react with strong tertiary bases such as 4-methylmorpholine to yield quaternary salts in which one benzyl group becomes attached to the nitrogen atom in the cation. Decomposition of these salts yields esters containing one benzyl group less than the original materials. The reaction is also applicable to substituted benzyl esters, but not, apparently, to phenyl or ethyl esters. It provides a flexible method for monodebenzylation, of value in the synthesis of unsymmetrical esters of polyphosphoric acids. Several new substituted benzyl phosphates are described.

THE investigations described in papers of this series had their origin in the need to devise suitable methods for the phosphorylation and polyphosphorylation of nucleosides and related compounds so that an attack by synthetic methods on the problem of nucleotide coenzymes and polynucleotides might become possible. Among the problems to be solved was the provision of methods whereby unambiguous syntheses of mono- and *as*-di-esters of pyrophosphoric and triphosphoric acid could be achieved. With this end in view we developed the use of dibenzyl chlorophosphonate as a phosphorylating agent for alcohols, since the initially formed dibenzyl phosphates offered a suitable starting point for pyrophosphate synthesis according to the scheme:

(1) $RO{\cdot}PO(O{\cdot}CH_2Ph)_2 \longrightarrow RO{\cdot}PO(O{\cdot}CH_2Ph){\cdot}OH$

(2) $RO{\cdot}PO(O{\cdot}CH_2Ph){\cdot}OAg + (Ph{\cdot}CH_2{\cdot}O)_2POCl \longrightarrow RO{\cdot}PO(O{\cdot}CH_2Ph)—O—PO(O{\cdot}CH_2Ph)_2$

$\downarrow$

$RO{\cdot}PO(OH)—O—PO(OH)_2$

Monodebenzylation (stage 1) in this process can be effected by hydrogenolysis (Atherton, Openshaw, and Todd, *J.*, 1945, 382) or by mild hydrolysis (Baddiley and Todd, *J.*, 1947, 648), and the general scheme indicated has been successfully applied to the synthesis of adenosine-5′ pyrophosphate (adenosine diphosphate) (Baddiley and Todd, *loc. cit.*). Extension of this synthetic route to the important adenosine-5′ triphosphate, although appearing at first sight straightforward, did not, in fact, prove to be so. The primary difficulty lay in the selective monodebenzylation of pyrophosphates—an essential step in extending the scheme outlined

above to the synthesis of triphosphates. We were unable to effect monodebenzylation of tetrabenzyl pyrophosphate, either by hydrolysis or hydrogenolysis, our experience with the latter method being the same as that of Deutsch and Fernö (*Nature*, **1945**, **156**, 604). It was therefore necessary to seek some new method of debenzylation, and the present paper records experiments which have led to the development of one satisfactory procedure which has been applied successfully in the synthesis of adenosine triphosphate (Baddiley, Michelson, and Todd, *Nature*, **1948**, **161**, 761; this vol., p. 582).

As described in Part IV of this series (Atherton, Howard, and Todd, *J.*, 1948, 220), in the course of experiments designed to increase the yield of product obtained on phosphorylating alcohols with dibenzyl chlorophosphonate, it was observed that the reagent underwent rapid and complete decomposition in the presence of a strong tertiary base; with *N*-methylmorpholine, for example, decomposition was very rapid and led to the formation of *N*-benzyl-*N*-methylmorpholinium chloride and, presumably, benzyl metaphosphate. The course of decomposition was held to be:

$$R_3N + (Ph\cdot CH_2\cdot O)_2POCl \longrightarrow [R_3N\cdot CH_2Ph]^+[O\cdot PO(O\cdot CH_2Ph)Cl]^-$$

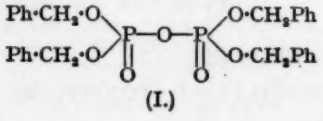
$$\downarrow$$

$$[R_3\overset{+}{N}\cdot CH_2Ph][\overset{-}{Cl}] + Ph\cdot CH_2\cdot OPO_2$$

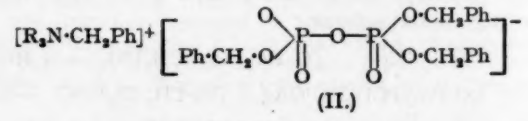
This decomposition, leading as it does to the removal of one benzyl group from dibenzyl chlorophosphonate, suggested that reaction with a strong base might well be applied to monodebenzylation of pyrophosphates, since these, as acyl phosphates, bear a formal resemblance to dibenzyl chlorophosphonate. This view was fully borne out by experiment. Tetrabenzyl pyrophosphate (I), when warmed with *N*-methylmorpholine, reacted readily, and the product—presumably the quaternary salt (II)—on treatment with water or dilute acid yielded tribenzyl pyrophosphate (III) as a colourless oil which formed a crystalline *monohydrate*; (III) was further characterised by preparation of its cyclo*hexylamine* salt.

The success of this experiment led us to apply a similar procedure to tribenzyl phosphate in the hope that here, too, monodebenzylation might be achieved. The view that reaction between a base and a phosphate might occur seemed not unreasonable since there are several recorded instances of alkylation of amines (Billman, Radike, and Mundy, *J. Amer. Chem. Soc.*, **1942**, **64**, 2977; cf. also Rueggeberg and Chernack, *ibid.*, **1948**, **70**, 1802), phenols (Noller and Dutton, *ibid.*, **1933**, **55**, 424), and alcohols (Toy, *ibid.*, **1944**, **66**, 499; Rueggeberg and Chernack, *loc. cit.*) with trialkyl phosphates, although the comparatively high temperatures employed might indicate that pyrolytic decomposition of the phosphate played an important part in the alkylations. Tribenzyl phosphate was accordingly refluxed with excess of *N*-methylmorpholine for two hours; on working up, dibenzyl hydrogen phosphate was isolated in excellent yield. In similar fashion *tri*-p-*nitrobenzyl phosphate*, *tri*-p-*bromobenzyl phosphate* and *tri*-(*5-chloro*-2 : 3-1′ : 3′-*dioxatetramethylenebenzyl*) *phosphate* (IV) yielded *di*-p-*nitrobenzyl hydrogen phosphate*, *di*-p-*bromobenzyl hydrogen phosphate*, and *di*-(*5-chloro*-2 : 3-1′ : 3′-*dioxatetramethylenebenzyl*) *hydrogen phosphate* respectively.

In the case of the tri-*p*-nitrobenzyl ester, the initially formed quaternary salt (V) was obtained in crystalline form, admixed with the *N*-methylmorpholine salt of di-*p*-nitrobenzyl hydrogen phosphate.

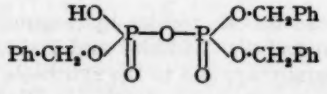


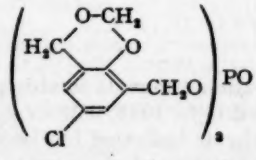
(I.)



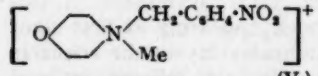
(II.)

(III.)





(IV.)



(V.)

$[O\cdot PO(O\cdot CH_2\cdot C_6H_4\cdot NO_2)_2]^-$ $[R_3N\cdot CH_2Ph]^+$ $[O\cdot P(O\cdot CH_2Ph_2]^-$

(VI.)

Additional examples recorded in the experimental section include monodebenzylation of dibenzyl *iso*amyl phosphate, *phenyl dibenzyl phosphate*, and 2-*hydroxy*cyclo*hexyl dibenzyl phosphate*. The last named compound was originally prepared by Dr. F. R. Atherton, in this laboratory, by the reaction of dibenzyl hydrogen phosphate with *cyclo*hexene oxide; the further development of this phosphorylation method in the preparation of sugar phosphates using anhydro-sugars as intermediates has also been studied and will form the subject of a separate communication. The quaternisation reaction * can also be applied to dibenzyl phosphite which reacts readily with *N*-methylmorpholine or triethylamine with production of monobenzyl phosphite ($Ph{\cdot}CH_2{\cdot}O{\cdot}PO_2H_2$), isolated as its *ammonium* salt. This is probably the most convenient method for preparing the monobenzyl phosphite which is an important intermediate in other phosphorylation studies now in progress and which we have hitherto prepared by partial hydrolysis of dibenzyl phosphite.

Since dibenzyl phosphite has few reactions of a tervalent phosphorus compound, it was of interest to examine the reaction of a tertiary base with tribenzyl phosphite in which the phosphorus atom is of necessity tervalent. It was not found possible to prepare this unstable ester in a pure condition, but by the use of material proved by assay to contain only some 13% of the dibenzyl ester it has been shown that it undergoes the normal quaternisation reaction with triethylamine, yielding dibenzyl phosphite as final product. The process of monodebenzylation by quaternisation can be applied only to neutral esters: esters such as dibenzyl hydrogen phosphate, which are ionic in character, do not undergo the reaction. That dibenzyl phosphite can be quaternised is, in our view, further evidence that it reacts as the neutral dibenzyl phosphonate [$HPO(O{\cdot}CH_2Ph)_2$]. It is of considerable interest that the quaternisation reaction applied to tribenzyl phosphite should yield dibenzyl phosphite; that the reaction stops at this stage is doubtless due to the dibenzyl phosphite being produced from an intermediate quaternary salt (VI) in which the dibenzyl phosphite is in the ionised form and so is resistant to further reaction with tertiary base. Only when the quaternary salt is decomposed will the dibenzyl phosphite revert to the normal non-ionised form.

The use of this reaction in the phosphorus series seems for all practical purposes to be confined to the removal of groups such as benzyl and substituted benzyl. Triphenyl phosphate did not react with *N*-methylmorpholine under the conditions employed with tribenzyl phosphate (cf. Morel, *Compt. rend.*, 1899, **128**, 50). When refluxed for long periods with *N*-methylmorpholine, triethyl phosphate gave only minute yields of diethyl phosphate; when the reaction was carried out at 165° in an autoclave, both di- and mono-ethyl phosphate were produced. The formation of monoethyl phosphate was unexpected, but it had earlier been observed that, when heated alone above 140°, tribenzyl phosphate appeared to decompose, yielding dibenzyl ether and benzyl metaphosphate. A similar decomposition of triethyl phosphate would give ethyl metaphosphate which is known to yield both di- and mono-ethyl phosphate on hydrolysis (Langheld, Oppmann, and Meyer, *Ber.*, 1912, **45**, 3753). In fact, virtually the same yield of these two products was obtained by heating triethyl phosphate alone at 165°; it is thus doubtful whether any appreciable quaternary salt formation occurs when it is heated with a tertiary base. Quaternary salt formation in the benzyl series may well be due, primarily, to the electrophilic character of the methylene group in the benzyl residue, and it is of interest that we were unable to effect any debenzylation by quaternisation in the case of dibenzyl aminophosphonate; this lack of reactivity may be due to the amino-group exercising its effect not only on the phosphorus atom but also upon the benzyl groups. Further studies on the mechanism and scope of the quaternisation reaction will be described in a later paper, but the present work provides a new and valuable method for the selective debenzylation of phosphites, phosphates, and pyrophosphates which should be capable of wide application.

Several substituted dibenzyl phosphates have been prepared and their reactions in various directions have been examined. The primary object in undertaking these studies was to ascertain whether or not the substituted benzyl esters offered marked advantages over the unsubstituted, either in ease of crystallisation or in reactivity. With this end in view, *ethyl di*-p-*nitrobenzyl phosphate*, 2-*hydroxy*cyclo*hexyl di*-p-*nitrobenzyl phosphate*, and 2-*hydroxy*cyclo*hexyl di*-p-*bromobenzyl phosphate* were prepared in addition to the other substituted benzyl esters mentioned earlier. Whilst it is true that these compounds showed some advantages (*e.g.*, in their ease of crystallisation) over corresponding unsubstituted benzyl esters, their expected slower rate of hydrogenolysis (cf. Baltzly and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 1984) and greater difficulty of preparation put them at a relative disadvantage for general use. We were unable to prepare α-naphthylmethyl phosphates, which might be expected to be more

* The sense in which the term " quaternisation " is used is explained in this vol., p. 583, footnote.

labile than benzyl phosphates (Baltzly and Buck, *loc. cit.*); all attempts to condense α-chloromethylnaphthalene with silver phosphate led to polymeric materials.

Attention is drawn to the fact that *cyclo*hexylamine gives highly crystalline salts with a number of the partly esterified phosphoric acids described in this paper as well as with dibenzyl hydrogen phosphate; these salts are useful for purposes of characterisation.

Experimental.

Tribenzyl Pyrophosphate.—*N*-Methylmorpholine (25 g.) was added to a solution of tetrabenzyl pyrophosphate (50 g.) in dry benzene (250 c.c.), and the mixture was refluxed for 2 hours. Benzene and *N*-methylmorpholine were removed under reduced pressure, and the residue washed twice with ether (250 c.c. in all). Aqueous silver nitrate (25 g. in 100 c.c. water) was added, followed by acetone (40 c.c.), and the mixture set aside at 0° for 3 hours with occasional shaking. The precipitated *silver tribenzyl pyrophosphate* (40 g.) was collected, washed with water and then with acetone, and dried in a desiccator at room temperature over phosphoric oxide (Found: Ag, 19·2. $C_{21}H_{21}O_7P_2Ag$ requires Ag, 19·4%). The silver salt (5·1 g.) was dissolved in chloroform (25 c.c.), and the solution saturated with hydrogen sulphide. Silver sulphide was filtered off, and the filtrate evaporated. The syrup so obtained was dissolved in a minimum quantity of moist ether and set aside at 0°; *tribenzyl pyrophosphate* separated as its *monohydrate* in colourless needles, m. p. 65° (3·85 g.) (Found: C, 53·3; H, 4·8. $C_{21}H_{22}O_7P_2,H_2O$ requires C, 54·0; H, 5·1%). When dried over phosphoric oxide at 100° the crystals changed to the syrupy anhydrous ester (Found: C, 55·4; H, 5·1. $C_{21}H_{22}O_7P_2$ requires C, 56·1; H, 4·9%) from which they could be regenerated by trituration with a little water.

Quaternisation of Tribenzyl Phosphate.—Tribenzyl phosphate (2 g.) was refluxed for 2 hours with *N*-methylmorpholine (25 c.c.), the excess of base removed under reduced pressure and the residual syrup washed with ether and then dissolved in benzene. The benzene solution was shaken twice with dilute sulphuric acid (3N) then with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in warm ether, and *cyclo*hexane was added until a cloudiness appeared. Dibenzyl hydrogen phosphate separated on standing (yield, 88%) as needles, m. p. and mixed m. p. 79—80°.

Addition of *cyclo*hexylamine (0·72 g.) to a solution of the above product (2 g.) in alcohol (10 c.c.) caused separation of cyclo*hexylamine dibenzyl phosphate*; recrystallised from alcohol it formed colourless needles, m. p. 173° (Found: C, 63·9; H, 7·2; N, 3·9. $C_{20}H_{28}O_4NP$ requires C, 63·6; H, 7·4; N, 3·7%).

2-*Hydroxy*cyclo*hexyl Dibenzyl Phosphate* (by Dr. F. R. Atherton).—Dibenzyl hydrogen phosphate (5·56 g.) was added to *cyclo*hexene oxide (2·0 g.) and dry carbon tetrachloride, and the mixture was set aside for 6 days with occasional shaking until the solution became homogeneous. Water (20 c.c.) was added, and then sufficient aqueous sodium hydroxide (1 c.c. of N) to make the aqueous layer alkaline to bromothymol-blue. The carbon tetrachloride phase was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in a minimum quantity of hot light petroleum (b. p. 60—80°), and the solution cooled. The *ester* separated as fine colourless needles (6·8 g., 91%), m. p. 78—80°, unchanged by further recrystallisation from light petroleum (Found: C, 64·2; H, 6·8. $C_{20}H_{25}O_5P$ requires C, 63·8; H, 6·6%).

The same ester was obtained in 83% yield by reaction of silver dibenzyl phosphate with 2-iodo*cyclo*hexan-1-ol.

Quaternisation of 2-*Hydroxy*cyclo*hexyl Dibenzyl Phosphate.*—A solution of the ester (2 g.) in *N*-methylmorpholine (25 c.c.) was boiled under reflux for 1 hour, moisture being excluded by a silica-gel tube. Excess of base was removed under reduced pressure, and the residue worked up as described in the case of tribenzyl phosphate. Unchanged starting material (0·29 g., 15%) was recovered, the main product being an oil (1·06 g., 69%) which did not crystallise. The oil was dissolved in aqueous ammonia (10 c.c. of 5%), excess of ammonia removed by a current of dry nitrogen, and a solution of silver nitrate (1 g.) in water (2 c.c.) added. The slightly opalescent mixture was set aside in a refrigerator for 48 hours, by which time *silver* 2-*hydroxy*cyclo*hexyl benzyl phosphate* had separated in colourless prisms (0·25 g.) which were collected, washed with water, alcohol, and ether, and dried under reduced pressure at 60° in absence of light (Found: C, 39·8; H, 5·0; Ag, 27·1. $C_{13}H_{18}O_5PAg$ requires C, 39·7; H, 4·6; Ag, 27·5%).

Quaternisation of Dibenzyl iso*Amyl Phosphate.*—The ester (4·57 g.; Atherton, Openshaw, and Todd, *J.*, 1945, 382) was dissolved in *N*-methylmorpholine (25 c.c.) and boiled under reflux for 2½ hours with exclusion of moisture. The yellowish solution was evaporated under reduced pressure, and the water-soluble oily residue shaken with a mixture of aqueous sodium hydroxide (20 c.c. of 5%) and ether (25 c.c.). The layers were separated, the aqueous one being again extracted with a further quantity of ether (25 c.c.). The aqueous layer was acidified with concentrated hydrochloric acid (10 c.c.), and the precipitated brown oil extracted with chloroform (3 × 25 c.c.). The chloroform extract was dried (Na_2SO_4), shaken with charcoal at room temperature, filtered, and evaporated. The pale brown oil so obtained (2·84 g.) was dissolved in dry ether (20 c.c.), and *cyclo*hexylamine (1·1 g.) in ether (5 c.c.) was added. There was considerable evolution of heat, and after a time the cyclo*hexylamine benzyl* iso*amyl phosphate* separated (3·65 g., 78%). The salt, thrice recrystallised from acetone, formed colourless needles, m. p. 131—132° (Found: C, 60·5; H, 9·0; N, 3·6. $C_{18}H_{32}O_4NP$ requires C, 60·6; H, 9·0; N, 3·9%).

Phenyl Dibenzyl Phosphate.—Dry powdered potassium phenoxide (8·6 g.) was placed in a flask cooled in an ice-bath, and an ice-cold solution of dibenzyl chlorophosphonate (prepared from 15 g. of dibenzyl phosphite in 150 c.c. carbon tetrachloride) was added gradually with stirring. The mixture was stirred at 0° for 6 hours and left overnight; no potassium chloride was precipitated. The solution was twice washed with aqueous sodium carbonate (250 c.c. of N) then with water, dried (Na_2SO_4), and evaporated, traces of benzyl chloride and benzyl alcohol being removed at 100°/1 mm. On addition of *cyclo*hexane to the residual oil, *phenyl dibenzyl phosphate* (11·9 g., 56%) separated. Recrystallised from light petroleum (b. p. 60—80°) it formed clusters of colourless needles, m. p. 42° (Found: C, 68·0; H, 5·7. $C_{20}H_{19}O_4P$ requires C, 67·8; H, 5·4%).

Quaternisation of Phenyl Dibenzyl Phosphate.—The ester (2·05 g.) was refluxed for 3 hours with *N*-methylmorpholine (25 c.c.), and the mixture worked up as described in the case of dibenzyl *iso*amyl phosphate (above). The crude oily acid (1·4 g.) was treated with *cyclo*hexylamine (525 mg.) in ether to give *cyclo*hexylamine phenyl benzyl phosphate which crystallised from ethanol–acetone in long silky needles, m. p. 145° (Found: C, 62·6; H, 7·3; N, 4·0. $C_{19}H_{26}O_4NP$ requires C, 62·8; H, 7·2; N, 3·9%).

Phenyl benzyl hydrogen phosphate itself did not crystallise, but it gave a *silver* salt, crystallising from water in colourless needles (Found: Ag, 28·8. $C_{13}H_{12}O_4PAg$ requires Ag, 29·0%). Catalytic hydrogenation of the free acid ester regenerated from the *cyclo*hexylamine salt yielded phenyl dihydrogen phosphate, m. p. 97—98° (Jacobsen, *Ber.*, 1875, **8**, 1521, gives m. p. 97—98°) which was further characterised as its cyclo*hexylamine* salt, m. p. 214—215° (colourless needles from ethanol) (Found: C, 53·3; H, 6·9; N, 5·5. $C_{12}H_{20}O_4NP$ requires C, 53·0; H, 7·3; N, 5·2%).

Tri-p-*nitrobenzyl Phosphate.*—A mixture of *p*-nitrobenzyl bromide (108 g.), silver phosphate (70 g.), and dry methyl cyanide (450 c.c.) was heated under reflux with vigorous stirring during 6 hours, light being excluded. The slightly yellow solution was filtered from silver bromide and allowed to cool; *tri*-p-*nitrobenzyl phosphate* then crystallised. Further quantities of the same compound could be obtained by extracting the crude silver bromide with hot ethyl acetate. The combined material was recrystallised from ethanol, and the ester was obtained as pale yellow plates, m. p. 127—128° (Found: C, 50·3; H, 3·9; N, 8·5. $C_{21}H_{18}O_{10}N_3P$ requires C, 50·1; H, 3·6; N, 8·4%) (yield, 72 g., 85%).

In order to obtain maximum yields in the above preparation vigorous stirring is essential, and methyl cyanide is the preferred reaction medium. Tri-*p*-nitrobenzyl phosphate is unaffected by 10 minutes' boiling with nitric acid (concentrated or dilute). It can be hydrogenated readily to phosphoric acid and *p*-toluidine, using a palladised charcoal catalyst at room temperature and atmospheric pressure.

Quaternisation of Tri-p-*nitrobenzyl Phosphate.*—The ester (2·0 g.) was dissolved in *N*-methylmorpholine (25 c.c.), and the solution heated with stirring on a boiling water-bath. After 10 minutes the solution became opalescent, and after 30 minutes pale yellow crystals separated. Heating was continued for 1¼ hours in all, and the crystalline precipitate (1·85 g.; m.p. 179—180°) was collected and well washed with light petroleum (b. p. 60—80°) to remove any adhering base. Attempts to recrystallise this material from methanol–ethylene dichloride mixtures yielded only oily products, so it was analysed directly [Found: C, 50·9; H, 5·2; N, 8·9. Calc. for the quaternary salt (V) $C_{36}H_{39}O_{11}N_4P$: C, 51·7; H, 4·8; N, 9·3%].

It was soon clear that this product could not be the pure salt (V), because, on decomposing a quantity (770 mg.) with dilute hydrochloric acid, di-*p*-nitrobenzyl hydrogen phosphate (495 mg.; m. p. 171—172°) was obtained. This amount of product would correspond to an acid content of 64·2% in the quaternary salt which, if it has structure (V), has, in fact, a theoretical content of only 61%. If as seems probable the impurity is the *N*-methylmorpholine salt of di-*p*-nitrobenzyl hydrogen phosphate, then the figures quoted would suggest that the material isolated in the quaternisation contains *ca.* 80% of (V) and 20% of the *N*-methylmorpholine salt; it is perhaps significant that such a mixture should give analytical values (C, 50·9; H, 4·9; N, 9·2%) in good agreement with the observed figures. To obtain further evidence for the nature of the crystalline reaction product of *N*-methylmorpholine and tri-*p*-nitrobenzyl phosphate a small portion was decomposed with dilute hydrochloric acid, the precipitated di-*p*-nitrobenzyl hydrogen phosphate filtered off, and the aqueous acid solution evaporated to dryness. On dissolving the residue in methanolic acetone and allowing it to stand, colourless crystals separated, m. p. 217—218°. Recrystallisation from acetone gave needles, m. p. 223°, undepressed in admixture with an authentic sample of N-p-*nitrobenzyl*-N-*methylmorpholinium chloride* (m. p. 227°), prepared from *N*-methylmorpholine and *p*-nitrobenzyl chloride (Found: C, 52·6; H, 6·2; N, 9·9. $C_{12}H_{17}O_3N_2Cl$ requires C, 52·8; H, 6·3; N, 10·3%).

In a separate experiment, tri-*p*-nitrobenzyl phosphate (15 g.) was heated with *N*-methylmorpholine (60 c.c.) at 80—85° during 2½ hours. The yellow crystalline precipitate was collected, washed, dissolved in water, and acidified with dilute hydrochloric acid. The crude acid which separated was purified by dissolving it in the minimum amount of aqueous sodium carbonate, boiling the solution with charcoal, filtering, and re-acidifying. The *di*-p-*nitrobenzyl hydrogen phosphate* so obtained crystallised from ethanol in yellow plates (9·0 g., 82%), m. p. 173—174° (Found: C, 45·6; H, 3·7; N, 7·3. $C_{14}H_{13}O_9N_2P$ requires C, 45·7; H, 3·6; N, 7·6%). The compound gives a crystalline *silver* salt (Found: Ag, 22·7; $C_{14}H_{12}O_9N_2PAg$ requires Ag, 22·7%) which is sparingly soluble in cold water (0·75 g. per 100 c.c.).

The yield of di-*p*-nitrobenzyl hydrogen phosphate obtained by quaternisation is considerably reduced when the reaction with *N*-methylmorpholine is carried out at the boiling point of the latter, owing to secondary decomposition.

Tri-p-*bromobenzyl Phosphate.*—A mixture of *p*-bromobenzyl bromide (110 g.; prepared in *ca.* 45% yield by bromination of *p*-bromotoluene in boiling carbon tetrachloride in presence of benzoyl peroxide), silver phosphate (62 g.), and methyl cyanide (500 c.c.) was heated under reflux with vigorous stirring for 1 hour. The product was isolated in the same way as the tri-*p*-nitrobenzyl ester (above). Recrystallised from ethyl acetate, *tri*-p-*bromobenzyl phosphate* (75 g., 84%) formed colourless needles, m. p. 132—133° (Found: C, 40·9; H, 3·0. $C_{21}H_{18}O_4PBr_3$ requires C, 40·7; H, 3·0%).

Di-p-*bromobenzyl Hydrogen Phosphate.*—Tri-*p*-bromobenzyl phosphate (15 g.) was heated on a boiling water-bath for 3 hours with *N*-methylmorpholine. Evaporation of the solution gave a resin which was dissolved in water and acidified with dilute hydrochloric acid. The precipitate was suspended in water (100 c.c.), and dissolved by adding sodium carbonate until the liquid was alkaline to phenolphthalein. The resulting solution of sodium salt was boiled with charcoal, filtered, cooled, and acidified with hydrochloric acid. *Di*-p-*bromobenzyl hydrogen phosphate* separated as colourless needles; recrystallised from ethanol, the product (8·3 g., 79%) had m. p. 155—156° (Found: C, 38·6; H, 3·3. $C_{14}H_{13}O_4Br_2P$ requires C, 38·6; H, 3·0%). The compound gave a sparingly soluble *silver* salt (Found: Ag, 19·5. $C_{14}H_{12}O_4Br_2PAg$ requires Ag, 19·9%). Removal of the *p*-bromobenzyl groups from the ester by catalytic hydrogenation is much slower than hydrogenolysis of dibenzyl hydrogen phosphate.

Tri-(5-*chloro*-2:3-1′:3′-*dioxatetramethylenebenzyl*) *Phosphate.*—5-Chloro-2:3-1′:3′-dioxatetramethylenebenzyl chloride (6·57 g.; Buehler, Bass, Darling, and Lubs, *J. Amer. Chem. Soc.*, 1940, **62**,

890) and silver phosphate (4·19 g.) were heated under reflux in benzene (70 c.c.) with vigorous stirring for 6 hours. The *ester* separated from the filtered solution on cooling, and was recrystallised from benzene. It formed colourless needles (5·1 g., 78%), m. p. 142—143° (Found: C, 50·4; H, 4·0. $C_{27}H_{24}O_{10}Cl_2P$ requires C, 50·2; H, 3·7%). The compound is rather sparingly soluble in most solvents, and appears to be dimorphous since at times it separated as needles, m. p. 157—158°; the two forms were interconvertible, but their stability under different conditions was not investigated. Even after repeated recrystallisation the ester resisted all attempts at catalytic hydrogenation.

Di-(5-chloro-2 : 3-1′ : 3′-dioxatetramethylenebenzyl) Hydrogen Phosphate.—The above tri-ester (2·36 g.) was heated on a boiling water-bath with *N*-methylmorpholine (20 c.c.) during 3 hours, and the product worked up as in the case of the *p*-bromobenzyl ester. The *product* crystallised from dioxan in colourless needles (1·22 g., 71%), m. p. 183—184° (Found: C, 46·6; H, 3·8. $C_{18}H_{17}O_8Cl_2P$ requires C, 46·7; H, 3·8%).

Attempted Quaternisation of Triethyl Phosphate.—Triethyl phosphate (9·1 g.) was refluxed with *N*-methylmorpholine (25 c.c.) for 84 hours with exclusion of moisture. Excess of base was removed under reduced pressure, leaving a brown oil which was dissolved in water, boiled with charcoal, filtered, and the filtrate made strongly alkaline with barium hydroxide. After removal of excess of barium by passing carbon dioxide through the solution and filtering, the solution was concentrated under reduced pressure to small bulk (20 c.c.), and ethanol (200 c.c.) was added. The aqueous ethanolic solution was evaporated until crystallisation set in. On standing, barium diethyl phosphate (260 mg., 2·4%) separated in long needles [Found: C, 22·1; H, 4·6; Ba, 30·4. Calc. for $Ba(C_4H_{10}O_4P)_2$: C, 21·7; H, 4·5; Ba, 30·9%].

The above experiment was repeated under more drastic conditions, heating being carried out in an autoclave at 165° for 48 hours. On addition of ethanol to the aqueous solution of the barium salts, a sparingly soluble salt separated when the ethanol concentration reached 30%; this salt (530 mg., 3·3%), from its analysis, was evidently barium ethyl phosphate (Found: C, 7·6; H, 2·6; Ba, 45·8. Calc. for $C_2H_5PO_4Ba,2H_2O$: C, 8·1; H, 3·0; Ba, 46·2%). Evaporation of the mother liquors from the sparingly soluble salt gave barium diethyl phosphate (740 mg., 6·1%) (Found: C, 22·1; H, 4·7; Ba, 30·4%).

A third experiment was carried out in which triethyl phosphate (9·1 g.) was heated alone at 165°. On working up in the manner of the earlier experiments, barium ethyl phosphate (450 mg.) and barium diethyl phosphate (740 mg.) were again obtained.

Ammonium Monobenzyl Phosphite.—(a) *By partial hydrolysis of dibenzyl phosphite.* A series of experiments on the hydrolysis of dibenzyl phosphite using N/70-sulphuric acid showed that one benzyl group was much more readily removed than the other. The following method was adopted for preparative work.

Dibenzyl phosphite (5·24 g.) was dissolved in aqueous dioxan (600 c.c. of 75%) containing sulphuric acid at a concentration of N/70. The solution was boiled under reflux in an oil-bath until titration of aliquots showed a rise in acidity corresponding to the removal of one benzyl group from the ester (1½ hours). The sulphuric acid was removed quantitatively with barium hydroxide, barium sulphate spun off, and the solution neutralised with ammonia. The neutralised solution was concentrated to small bulk (80 c.c.) in a nitrogen atmosphere under reduced pressure, acidified with dilute hydrochloric acid, and extracted with chloroform (2 × 100 c.c.). The dried chloroform extract was then concentrated to 60 c.c., cooled to 0°, and saturated with gaseous ammonia. *Ammonium monobenzyl phosphite* separated and was recrystallised from "cellosolve"–dioxan. It formed colourless needles (1·74 g., 46%), m. p. 154° [Found: C, 44·6; H, 6·4; N, 7·4. $NH_4(C_7H_9O_3P)$ requires C, 44·4; H, 6·4; N, 7·4%].

Monobenzyl phosphite itself was obtained as a pale yellow oil by acidifying an aqueous solution of the ammonium salt and extracting with chloroform. As it could not be purified by distillation or crystallisation, evidence for its identity was obtained by treatment with phenyldiazomethane. The product was evidently dibenzyl phosphite, for with carbon tetrachloride and ammonia, it gave dibenzyl aminophosphonate (overall yield on ammonium salt, 72%).

(b) *By quaternisation of dibenzyl phosphite.* Dibenzyl phosphite (2 g.) was dissolved in triethylamine (20 c.c.), and the solution heated under reflux with stirring in a nitrogen atmosphere for 1 hour, during which time it separated into two layers. Excess of base was removed under reduced pressure, and the residual oil was shaken with aqueous sodium hydroxide (10 c.c. of 5%) and ether (25 c.c.), and the layers separated. The aqueous layer was washed with ether, then acidified with concentrated hydrochloric acid (2 c.c.) and extracted with chloroform (3 × 25 c.c.). The combined chloroform extracts were dried (Na_2SO_4), concentrated to smaller bulk (25 c.c.), and cooled to 0°. When ammonia was passed through the solution, *ammonium monobenzyl phosphite* separated (1·25 g., 87%). Recrystallised from "cellosolve"–dioxan, the salt formed long needles, m. p. 154°, undepressed in admixture with an authentic specimen prepared by partial hydrolysis of dibenzyl phosphite (see above).

When the period of refluxing was extended to 2 hours in the above experiment, the yield of pure product decreased to 51%; by allowing dibenzyl phosphite to stand at room temperature with *N*-methylmorpholine for 6 days a 73% yield of the above ammonium salt was obtained.

Tribenzyl Phosphite.—A solution of benzyl alcohol (32·4 g., 3 mols.) in pyridine (23·7 g., 3 mols.) and dry ether (50 c.c.) was cooled in an ice–salt mixture, and a solution of phosphorus trichloride (13·75 g., 1 mol.) in dry ether (20 c.c.) added gradually during 30 minutes, the mixture being vigorously stirred and moisture excluded by means of a silica-gel tube. Pyridine hydrochloride began to separate almost at once, and, after the mixture had been stirred at 0° for a further 2 hours, it was filtered (wt. of precipitated pyridine hydrochloride, 31·2 g., 91%), and the filtrate evaporated in a stream of dry oxygen-free nitrogen, any remaining traces of pyridine and phosphorus trichloride being removed at 70° under reduced pressure. The residual crude tribenzyl phosphite was a colourless oil (34·2 g.) which had a faint odour of dibenzyl phosphite. In order to determine the amount of dibenzyl phosphite in it, a portion (10·4 g.) was submitted to reaction with carbon tetrachloride and ammonia as described by Atherton, Openshaw, and Todd (*J.*, 1945, 660). From the reaction, dibenzyl aminophosphonate (1·38 g., m. p. 103°) was obtained corresponding to a content of 13% dibenzyl phosphite in the original ester (trialkyl phosphites do not react with carbon tetrachloride and ammonia).

The crude tribenzyl phosphite could not be purified by distillation in a nitrogen atmosphere, the product, which boiled at 225—230°/0·05 mm., containing 34% of dibenzyl phosphite. Purification by low-temperature crystallisation from acetone at −60° gave a product, possibly the pure ester, which liquefied at room temperature, and on exposure to air resolidified rapidly; the solid obtained had m. p. 59—61°, and, when recrystallised from *cyclo*hexane gave needles, m. p. 64°, undepressed in admixture with an authentic specimen of tribenzyl phosphate (m. p. 64°). It was accordingly decided to use the crude tribenzyl phosphite directly for quaternisation experiments.

Quaternisation of Tribenzyl Phosphite.—The crude tribenzyl ester (10·3 g. containing *ca.* 13% dibenzyl phosphite) was dissolved in triethylamine (25 c.c.), and the solution refluxed for 1 hour in a stream of dry nitrogen. During the reaction, the solution separated into a colourless upper layer and a faintly yellow lower layer. Excess of base was removed under reduced pressure in a stream of nitrogen, the mixture foaming a good deal during this operation. The residual yellow oil dissolved completely in benzene (50 c.c.), and the benzene solution was shaken with dilute hydrochloric acid (2 × 40 c.c. of 2N), then with water, and dried. The benzene solution was then diluted with carbon tetrachloride (50 c.c.), and gaseous ammonia was passed through it for 35 minutes. Ammonium chloride (0·81 g.) was precipitated, and, from the benzene–carbon tetrachloride solution, dibenzyl aminophosphonate was obtained by evaporation. Recrystallised from carbon tetrachloride it had m. p. 102—103°, undepressed in admixture with an authentic specimen (m. p. 103—104°). The yield of dibenzyl aminophosphonate was 3·7 g. which, had the original tribenzyl phosphite been 100% pure and the conversion of dibenzyl phosphite into dibenzyl aminophosphonate quantitative, would correspond to a 46% yield in the quaternisation reaction.

2-*Hydroxy*cyclo*hexyl Di*-p-*nitrobenzyl Phosphate.*—(*a*) Silver di-*p*-nitrobenzyl phosphate (1·78 g.) and 2-iodo*cyclo*hexan-1-ol (0·95 g.) were heated under reflux in methyl cyanide (15 c.c.) during 1 hour. The cooled mixture was filtered, the precipitated silver iodide being well washed with methyl cyanide. The combined filtrate and washings were evaporated, and the residue was dissolved in hot ethanol (7 c.c.), boiled for a few minutes with charcoal, and filtered. The crystalline product (1·55 g., 89%) was precipitated by gradual addition of water and recrystallised from carbon tetrachloride. It formed pale yellow needles, m. p. 112—113° (Found: C, 51·9; H, 4·9; N, 5·8. $C_{20}H_{23}O_9N_2P$ requires C, 51·5; H, 5·0; N, 6·0%).

(*b*) Di-*p*-nitrobenzyl hydrogen phosphate (3·68 g.) and freshly distilled *cyclo*hexene oxide (1·0 g.) were dissolved in pure dioxan (30 c.c.), and the solution heated on the water-bath for 2 hours. Solvent was removed under reduced pressure, and the crystalline residue washed with water then with dilute ammonia and again with water. The crude product (4·45 g., 95%) had m. p. 110—112°, raised by one recrystallisation from a minimum quantity of ethanol to 112—113°, undepressed in admixture with material prepared by method (*a*).

Di-p-*nitrobenzyl Ethyl Phosphate.*—Silver di-*p*-nitrobenzyl phosphate (8 g.) was added to a solution of ethyl iodide (2·5 c.c.) in dry methyl cyanide (60 c.c.), and the mixture was refluxed for 15 minutes. The filtered solution was evaporated under reduced pressure, and the semi-crystalline residue dissolved in ethanol. The ethanolic solution was boiled with charcoal, filtered, cooled, and the *ester* precipitated in crystalline form by very cautious addition of water. Recrystallised from benzene–*cyclo*hexane, di-*p*-nitrobenzyl ethyl phosphate formed pale yellow needles (5·83 g., 88%), m. p. 65—66° (Found: C, 48·6; H, 4·6; N, 7·4. $C_{16}H_{17}O_8N_2P$ requires C, 48·5; H, 4·3; N, 7·1%).

A portion of the ester (3·5 g.) was dissolved in aqueous ethanol (200 c.c. of 80%) and hydrogenated at room temperature under atmospheric pressure, using a palladium oxide catalyst (0·05 g.); hydrogenation was complete in 1½ hours (hydrogen uptake *ca.* 1700 c.c.). After removal of catalyst by filtration, the solution was neutralised with barium hydroxide, *p*-toluidine removed by steam distillation, and barium ethyl phosphate isolated as its crystalline hydrate by concentration to small bulk (20 c.c.) and addition of ethanol. The anhydrous salt (2·07 g., 89%) was obtained by drying at 105—110°/0·1 mm. (Found: Ba, 52·0. Calc. for $C_2H_5O_4PBa$: Ba, 52·6%).

2-*Hydroxy*cyclo*hexyl Di*-p-*bromobenzyl Phosphate.*—This compound was prepared by two methods as described for the corresponding *p*-nitrobenzyl ester. Method (*a*) yielded colourless needles (yield, 73%), m. p. 104—105° from *cyclo*hexane (Found: C, 44·7; H, 4·5. $C_{20}H_{23}O_5Br_2P$ requires C, 45·0; H, 4·3%). The crude product from method (*b*) (yield, 95%) had m. p. 112—113°, undepressed with the product made by method (*a*). This unusual behaviour may be connected with the obvious possibility of a mixture of stereoisomers being present in the initial product.

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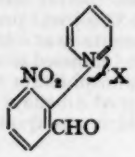
177. *A Novel Synthesis of Some Quinoline Derivatives.*

By DOUGLAS ALLAN and JAMES D. LOUDON.

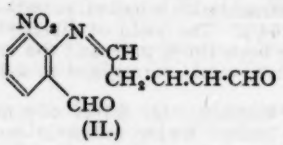
Derivatives of benzaldehyde or benzophenone, which carry a sufficiently reactive chloro- or toluene-*p*-sulphonyloxy-substituent in the ortho-position, are converted into derivatives of β-3-quinolylacraldehyde *via* pyridinium salts of type (I). A note on the nitration of *o*-hydroxyacetophenone is appended.

DURING the preparation of the *toluene*-p-*sulphonyl* derivative of 3-nitrosalicylaldehyde, using pyridine as solvent, it was observed that the ester readily reacted even with the cold solvent to

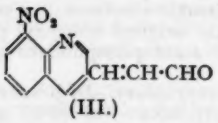
form a pyridinium salt. The salt was difficult to isolate in solid form but was conveniently prepared in aqueous solution. The *toluene*-p-*sulphonyl* derivative of 5-nitrosalicylaldehyde, although less reactive towards pyridine, yielded a crystalline pyridinium salt when its solution in pyridine was heated under reflux. The addition of alkali to aqueous solutions of these salts initiates a remarkably rapid series of changes resulting in the precipitation of compounds which are considered to be β-3-(8-*nitroquinolyl*)- and β-3-(6-*nitroquinolyl*)-*acraldehyde* respectively (cf. III). The structures assigned to these compounds are based on analogy with the well-known opening of the pyridine ring in 2 : 4-dinitrophenylpyridinium chloride (Zincke, *Annalen*, 1904, **330**, 361; **333**, 296; 1905, **338**, 107; **341**, 365) whereby in the present cases an intermediate such as (II) is made available for cyclisation to the quinoline (III).



(I.)



(II.)



(III.)

Extensive confirmation of the structure of these products has been obtained from a study of the compounds themselves and may be illustrated with reference to the product (III) derived from pyridine and 3-nitrosalicylaldehyde. (*a*) Oxidation with nitric acid removed two carbon atoms with formation of a *carboxylic acid*, which lost carbon dioxide when heated at its melting point and gave 8-nitroquinoline, identified by direct comparison with an authentic specimen. Accordingly, the presence of the quinoline ring with a side-chain in the heterocyclic nucleus may be inferred. (*b*) The compound was a feeble base which reacted with carbonyl reagents : a *phenylhydrazone* rather than a pyrazoline derivative appeared to be formed in reaction with phenylhydrazine. (*c*) By the action of acetic anhydride and a trace of sulphuric acid there was produced a *diacetate* from which the parent compound was regenerated by hydrolysis with dilute acid. This behaviour, together with the reducing properties of the compound, indicates the presence of an aldehydic group, but attempts to prepare the corresponding acid by mild oxidation have not been successful. (*d*) Addition of bromine resulted in formation of an unstable, pale yellow *dibromide* which, by shaking with cold aqueous sodium carbonate, readily eliminated hydrogen bromide to give a *monobromo-substitution* product. The latter retained the power of forming a *diacetate* and, on oxidation, yielded the nitroquinolinecarboxylic acid already obtained from (III). The production in this way of α-bromo-β-3-(8-nitroquinolyl)acraldehyde from the dibromide of (III) is a normal consequence of the structural features of the acraldehyde side-chain although it affords an interesting contrast to the regeneration of β-2-quinolylacrylic acid from the corresponding dibromide under similar conditions (Alberts and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 1284).

The scope of the reaction as a synthesis of hitherto inaccessible derivatives of quinoline is obviously conditioned by the availability of salts of type (I). In practice, the actual isolation of these salts is unnecessary, and in most of the cases examined an aqueous extract of the pyridine reaction products was directly employed for conversion into the quinoline. Depending on the reactivity of the toluene-*p*-sulphonic esters, these extracts were prepared either in one stage by the interaction of the sulphonyl chloride and the phenolic aldehyde in pyridine or by heating the pre-formed ester with pyridine. Appropriately substituted halogenobenzenes may also be used ; for example, 2-chloro-5-nitrobenzaldehyde when heated with pyridine afforded an aqueous extract from which β-3-(6-nitroquinolyl)acraldehyde was obtained. Salt formation is facilitated by the second nitro-group in 3 : 5-dinitrosalicylaldehyde from which β-3-(6 : 8-*dinitroquinolyl*)*acraldehyde* was readily prepared. On the other hand, replacement of the aldehydic by a ketonic function in the starting material is unfavourable to the reaction, for although β-3-(6 : 8-*dinitro*-4-*phenylquinolyl*)*acraldehyde* was readily obtained from 2-chloro- or 2-hydroxy-3 : 5-dinitrobenzophenone, yet little or no reaction occurred with 2-chloro-5-nitrobenzophenone. Again, from the *toluene*-p-*sulphonyl* derivatives of 3-nitro- and 5-nitro-2-hydroxyacetophenone—materials which contain potentialities for the ultimate synthesis of phenanthridines—only traces of compounds, apparently of a different type, were obtained. In no case was it possible to isolate crystalline products when α-picoline was used in place of pyridine in these reactions.

Note on the Nitration of o-*Hydroxyacetophenone.*—There appears to be some confusion in the literature regarding the 3- and 5-nitro-2-hydroxyacetophenones which were required for the

above investigation. By direct nitration of 2-hydroxyacetophenone in acetic acid, Wittig (*Annalen*, 1925, **446**, 181) isolated in small yield a steam-volatile nitro-ketone of m. p. 98·5—99·5° which he described as 3-nitro-2-hydroxyacetophenone, presumably because 3-nitrosalicylic acid was also isolated as a by-product. Lindemann and Romanoff (*J. pr. Chem.*, 1929, **122**, 214), who state that the phenolic ketone is destroyed by direct nitration, nitrated the oxime and, after separation and hydrolysis, obtained as main product a nitro-ketone (A) of m. p. 111—112° (oxime, m. p. 231°) together with a small quantity of a nitro-ketone (B) of m. p. 89—90° (oxime, m. p. 182°). Since the oxime of (A) afforded the known 5-nitro-3-methylbenz*iso*oxazole, (A) was oriented as 5-nitro-2-hydroxyacetophenone and, by exclusion, (B) was 3-nitro-2-hydroxyacetophenone. Repetition of Lindemann and Romanoff's work gave nitrated oximes of the recorded m. p.s but on hydrolysis (A) was obtained having m. p. 98—99°. It was identical with a steam-volatile nitro-ketone obtained by modifying Wittig's method of direct nitration and its orientation as the 5-nitro-isomer was confirmed by oxidation to 5-nitrosalicylic acid. The 3-nitro-isomer, obtained as subsidiary product both from the direct and from the indirect method of nitration, had m. p. 83°. All attempts to dinitrate *o*-hydroxyacetophenone either directly or stepwise failed, the only product isolated being picric acid.

Experimental.

Toluene-p-*sulphonate of* 3-*Nitrosalicylaldehyde*.—Sodium carbonate (0·32 g.) was added to a suspension of the aldehyde (0·5 g.) and toluene-*p*-sulphonyl chloride (0·6 g.) in hot water (25 c.c.) and the mixture was heated under reflux for one hour. The *ester* formed colourless crystals, m. p. 131° from benzene (Found: C, 52·5; H, 3·5. $C_{14}H_{11}O_6NS$ requires C, 52·3; H, 3·4%).

β-3-(8-*Nitroquinolyl*)*acraldehyde*.—(*a*) 3-Nitrosalicylaldehyde (5 g.), dissolved in cold, anhydrous pyridine (15 c.c.), was treated with toluene-*p*-sulphonyl chloride (6 g.) added portionwise so that the temperature remained below 27°. After 12 hours at room temperature the mixture was poured into dilute hydrochloric acid and ice, whereupon the above toluene-*p*-sulphonate separated (3·3 g., m. p. and mixed m. p. 130—131°). The clear yellow filtrate was neutralised by dropwise addition of dilute sodium hydroxide until a transient red colour just persisted. The quinolylacraldehyde which separated formed colourless needles (2·3 g.), m. p. 201—202°, from acetic acid (charcoal).

(*b*) When the pyridine reaction mixture was gently warmed (40°) for a few minutes and then allowed to cool before being worked up, the yield of the ester was diminished and a correspondingly greater, but less pure quantity of the *quinoline* derivative was obtained (Found: C, 63·2; H, 3·8; N, 12·1. $C_{12}H_8O_2N_2$ requires C, 63·2; H, 3·5; N, 12·3%). It gave an *oxime*, golden-yellow plates, m. p. 250° (decomp.), from acetic acid, when heated (4 hours) with hydroxylamine in ethanol–dioxan (Found: C, 59·1; H, 4·2; N, 17·2. $C_{12}H_9O_2N_3$ requires C, 59·3; H, 3·7; N, 17·3%); a *phenylhydrazone*, orange crystals, m. p. 205°, from acetic acid, for which Raiford and Petersen's pyrazoline-test (*J. Org. Chem.*, 1937, **1**, 544) was negative (Found: N, 17·7. $C_{18}H_{14}O_2N_4$ requires N, 17·4%); and a *diacetate*, colourless needles, m. p. 136—137°, formed when a small drop of concentrated sulphuric acid was added to a suspension of the acraldehyde in cold acetic anhydride and the whole, after 12 hours, was poured into water (Found: C, 58·45; H, 4·2. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·2%). The parent acraldehyde was regenerated when a solution of the diacetate in cold concentrated hydrochloric acid was allowed to stand for 1 hour and was then poured into water.

αβ-Dibromo-β-3-(8-*nitroquinolyl*)*propaldehyde* was obtained as yellow needles, m. p. 220° (decomp.), from warm (not boiling) acetic acid, when a solution containing molar proportions of the components in acetic acid was heated (10 minutes) at 100° and allowed to cool (Found: C, 37·1; H, 2·1. $C_{12}H_8O_2N_2Br_2$ requires C, 37·1; H, 2·1%).

α-Bromo-β-3-(8-*nitroquinolyl*)*acraldehyde* was obtained when the above dibromide was shaken with aqueous sodium carbonate or was subjected to prolonged heating in acetic acid. It formed colourless needles, m. p. 183° from dilute acetic acid (Found: C, 46·55; H, 2·2. $C_{12}H_7O_2N_2Br$ requires C, 46·9; H, 2·3%); it yielded a *diacetate*, m. p. 150—151° (Found: C, 47·1; H, 3·2. $C_{16}H_{13}O_6N_2Br$ requires C, 46·95; H, 3·2%), and when oxidised with concentrated nitric acid yielded the following acid.

8-*Nitroquinoline*-3-*carboxylic Acid*.—A solution of *β*-3-(8-nitroquinolyl)acraldehyde in nitric acid (*d* 1·42) was carefully heated on the water-bath and the vigorous reaction which ensued was controlled by occasional cooling. Heating was continued for 1 hour, water was added, and after most of the nitric acid had been distilled off, the *acid* separated on cooling and formed slender needles, m. p. 285° (with gas evolution) from ethanol (Found: C, 54·85; H, 3·0; N, 12·7. $C_{10}H_6O_4N_2$ requires C, 55·0; H, 2·75; N, 12·8%). When sublimed at its m. p. it yielded a mixture of unchanged acid, extracted in dilute alkali, and 8-nitroquinoline, identified by m. p. and mixed m. p. 88—89° with an authentic specimen.

Toluene-p-*sulphonate of* 5-*Nitrosalicylaldehyde*.—(*a*) The aldehyde (2 g.), toluene-*p*-sulphonyl chloride (2·4 g.), and dimethylaniline (10 c.c.) were heated at 100° for 1 hour. The solid *ester* obtained on pouring into dilute hydrochloric acid was crystallised from acetic acid (charcoal) and had m. p. 97—98° (Found: C, 52·4; H, 3·6. $C_{14}H_{11}O_6NS$ requires C, 52·3; H, 3·4%). (*b*) The sulphonyl chloride (30 g.) was added to a warm solution of the aldehyde (25 g.) in pyridine (25 c.c.) and, after being heated at 100° for a few minutes, the mixture was left at room temperature for 12 hours and was then poured into dilute hydrochloric acid. The purified ester weighed 32 g. (67%) and the aqueous filtrate yielded some *β*-3-(6-nitroquinolyl)acraldehyde (below).

(4-*Nitro*-2-*formylphenyl*)*pyridinium Toluene*-p-*sulphonate*.—A solution of the preceding ester (4 g.) in anhydrous pyridine (4 c.c.) and benzene (3 c.c.) was heated under reflux for 2 hours. After cooling, the crystalline *salt* was collected, washed with dry ether, and recrystallised from a very little warm

(not boiling) water. It formed colourless needles, m. p. 215—216° (Found : C, 56·8; H, 4·1; N, 6·8. $C_{19}H_{16}O_6N_2S$ requires C, 57·0; H, 4·0; N, 7·0%).

β-3-(6-Nitroquinolyl)acraldehyde.—The aqueous solution (clarified if necessary by charcoal) obtained (*a*) as filtrate from the above ester of 5-nitrosalicylaldehyde, (*b*) by dissolving the above pyridinium salt in water, or (*c*) by heating either 2-chloro-5-nitrosalicylaldehyde or the above ester of 5-nitrosalicylaldehyde with pyridine at 100° for 2 hours and adding them to cold dilute hydrochloric acid, was treated dropwise with 10% sodium hydroxide solution until no further change of colour occurred. After standing for 30 minutes, the mixture was again made slightly acid to coagulate the solid, which was then collected and crystallised from acetic acid. The *acraldehyde*, small pale yellow clusters of m. p. 247° (Found: C, 63·1; H, 3·2; N, 12·3. $C_{12}H_8O_3N_2$ requires C, 63·2; H, 3·5; N, 12·3%), gave a *phenylhydrazone*, orange-red needles, m. p. 226—228° (decomp.) (Found : C, 67·9; H, 4·4; N, 17·6. $C_{18}H_{14}O_2N_4$ requires C, 68·1; H, 4·3; N, 17·4%), and a colourless diacetate, m. p. 188°, for which persistently high values for carbon were obtained on analysis.

6-Nitroquinoline-3-carboxylic acid, m. p. 300° (decomp.), from ethanol–acetic acid, was prepared by oxidising *β*-3-(6-nitroquinolyl)acraldehyde as in the case of its isomer (Found : C, 55·3; H, 3·1; N, 12·8. $C_{10}H_6O_4N_2$ requires C, 55·0; H, 2·75; N, 12·8%), and yielded 6-nitroquinoline, m. p. and mixed m. p. 150—151°, on sublimation at 300—310°.

β-3-(6 : 8-Dinitroquinolyl)acraldehyde.—Toluene-*p*-sulphonyl chloride (1 g.) was added at 0° to the suspension resulting from mixing 3 : 5-dinitrosalicylaldehyde (1 g.) and pyridine (10 c.c.), and the whole, after being vigorously shaken at room temperature for 30 minutes, was kept for several hours and then poured into dilute hydrochloric acid. The resulting aqueous solution was made alkaline with sodium carbonate, warmed to 60°, and the collected precipitate was crystallised first from acetic acid and then from benzene. The *aldehyde* formed fine colourless needles, m. p. 241° (Found : C, 52·9; H, 2·4; N, 15·2. $C_{12}H_7O_5N_3$ requires C, 52·7; H, 2·6; N, 15·0%), and gave a *phenylhydrazone*, dark red crystals, m. p. 245° (decomp.) from benzene (Found : C, 59·7; H, 3·8; N, 19·3. $C_{18}H_{13}O_4N_5$ requires C, 59·5; H, 3·6; N, 19·3%), and a *diacetate*, colourless needles, m. p. 177—178° from benzene (Found : C, 51·4; H, 3·5. $C_{16}H_{13}O_5N_3$ requires C, 51·2; H, 3·5%).

α-Bromo-β-3-(6 : 8-dinitroquinolyl)acraldehyde.—A solution of the preceding aldehyde (1 g.) in acetic acid was treated with the calculated quantity of bromine and heated at 100° for a few minutes. The dibromide, bright yellow needles, m. p. 225° (decomp.), which separated on cooling, was rather unstable and was converted into the corresponding *α-bromo-acraldehyde* by shaking with cold dilute sodium carbonate solution. The latter compound formed fine colourless needles, m. p. 238° (decomp.) from acetic acid (Found : C, 41·4; H, 1·6. $C_{12}H_6O_5N_3Br$ requires C, 40·9; H, 1·7%).

6 : 8-Dinitroquinoline-3-carboxylic acid, pale yellow crystals of m. p. 301—302° (decomp.), was obtained by oxidising the corresponding acraldehyde with nitric acid (Found : C, 44·0; H, 2·0. $C_{10}H_5O_6N_3,\frac{1}{2}H_2O$ requires C, 44·1; H, 2·2%), and yielded 6 : 8-dinitroquinoline, m. p. 151° from benzene, on decarboxylation by sublimation.

β-3-(6 : 8-Dinitro-4-phenylquinolyl)acraldehyde.—(*a*) A solution of 2-chloro-3 : 5-dinitrobenzophenone (5 g.) in dry pyridine (15 c.c.) was heated at 100° for 30 minutes. After being cooled, added to dilute hydrochloric acid, and clarified with charcoal, the resulting aqueous solution was slowly treated with dilute sodium hydroxide until no further colour change occurred. After 1 hour the precipitate was collected and formed straw-coloured plates, m. p. 243—244°, from acetic acid (Found : C, 62·0; H, 3·2; N, 12·2. $C_{18}H_{11}O_5N_3$ requires C, 61·9; H, 3·15; N, 12·0%). (*b*) The same compound, m. p. and mixed m. p. 242—243°, was also obtained from the aqueous extract, prepared in the usual way, from the interaction of toluene-*p*-sulphonyl chloride (0·37 g.) and 3 : 5-dinitro-2-hydroxybenzophenone (0·6 g.) in anhydrous pyridine (5 c.c.).

Nitration of o-*Hydroxyacetophenone.*—Nitric acid (30 g.; *d*, 1·52) was slowly added to a stirred solution of the ketone (20 g.) in acetic acid (100 c.c.) kept below 12°. The temperature of the resulting mixture was then allowed to rise spontaneously to 50—55° (caution) whereupon the mixture was quickly poured into crushed ice. The solidified oil was collected and, together with material recovered from a benzene extract of the aqueous mother-liquor, was distilled in steam. The first runnings, which contained some oil, were discarded, and the solid which separated from the later distillate (*ca.* 6 l.) yielded 5-nitro-2-hydroxyacetophenone as colourless needles (4—5 g.), m. p. 98—99° from ethanol (Found : C, 53·3; H, 4·0; N, 7·9. Calc. for $C_8H_7O_4N$: C, 53·05; H, 3·9; N, 7·75%), identical with a specimen prepared by acid-hydrolysis of the oxime of m. p. 131° (Lindemann and Romanoff, *loc. cit.*) and oxidised (0·1 g.) by boiling (30 minutes) with dilute nitric acid (10 c.c.) to 5-nitrosalicylic acid, m. p. and mixed m. p. 228—229°. The residue in the steam-distillation flask afforded 3-nitro-2-hydroxyacetophenone, which was dissolved out in benzene and recovered from an alkaline extract of the solution. This compound formed pale yellow needles (0·5 g.) from ethanol, m. p. 82—83° (Found : C, 53·2; H, 3·9; N, 7·7%), and was identical with a specimen prepared from the oxime of m. p. 182° (*loc. cit.*). A mixture of the 3- and the 5-nitro-isomer (4 g., m. p. 60—65°) was recovered in benzene from the aqueous portion of the steam-distillate and was partly separated by renewed distillation in steam. Attempts to convert it directly into 3 : 5-dinitro-2-hydroxyacetophenone were unsuccessful.

*Toluene-*p*-sulphonate of 3-Nitro-2-hydroxyacetophenone.*—Toluene-*p*-sulphonyl chloride (0·2 g.) was added to a solution of the nitro-ketone in pyridine at 0°. After 24 hours at room temperature, the mixture was poured into dilute hydrochloric acid, and the solidified *ester*, m. p. 98—99° from ethanol, was collected (Found : C, 53·8; H, 3·7. $C_{15}H_{13}O_6NS$ requires C, 53·7; H, 3·9%). The filtrate, treated with dilute sodium hydroxide until the red colour was just permanent, gave a felted mass of purplish crystals, m. p. 113—115° from benzene–petroleum (Found : C, 64·6; H, 3·85; N, 11·45. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·1; N, 11·6%). This *compound*, which differed from the others of the present series in the intensity of its colour (almost black), was very sparingly soluble in dilute acids but was obtained in such small quantity that further investigation was not possible.

*Toluene-*p*-sulphonate of 5-Nitro-2-hydroxyacetophenone.*—This *ester*, m. p. 93—94° from ethanol, was obtained from its components as in the previous experiment (Found : C, 54·0; H, 3·9%), and the water-soluble product of the reaction, after the usual treatment and attempted purification on alumina, gave

only traces of a crystalline material. Equally unpromising results were obtained, both here and in the previous case, from experiments in which the pre-formed esters were heated in pyridine.

We thank the Carnegie Trust for the Universities of Scotland for a Scholarship which has enabled one of us (D. A.) to take part in this work, also Mr. W. F. Kier who carried out some of the preliminary experiments.

UNIVERSITY OF GLASGOW. [*Received, September 15th*, 1948.]

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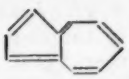
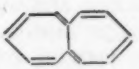
178. *Cyclic Conjugated Polyenes. Part I.* 1 : 2-*Benzazulene.*

By J. R. NUNN and W. S. RAPSON.

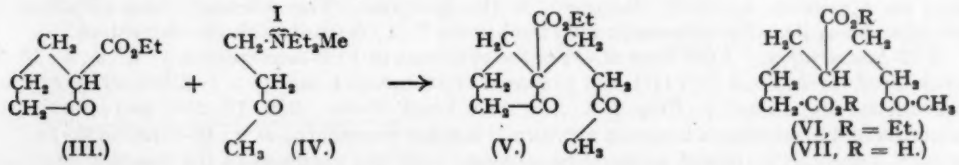
1 : 2-*Benzazulene* has been synthesised by two methods. The first method is an extension of an azulene synthesis based upon the ring expansion of hexahydroindan-5-one with diazomethane to yield decahydroazulones which are reduced and dehydrogenated to yield the azulenes themselves. The second method is an application of St. Pfau and Plattner's azulene synthesis (*Helv. Chim. Acta*, 1939, **22**, 202) which begins with the action of diazoacetic ester on fluorene. 1 : 2-Benzazulene is a deeply coloured, stable, crystalline substance showing many of the attributes of the azulenes themselves. It has been characterised by the formation of molecular complexes with 1 : 3 : 5-trinitrobenzene and 2 : 4 : 6-trinitrotoluene, and as a first step in its physical examination its visible and ultra-violet absorption spectra are recorded.

IN view of the interest that has been focussed for so many years on the problem of the structure and stability of benzenoid compounds, it is perhaps surprising that so little attention has been paid to analogous cyclic conjugated polyene structures, some of which may constitute new aromatic types (cf. Baker, *J.*, 1945, 258). Amongst such structures, that of azulene (I) is of particular interest, but although much attention has been paid to the synthesis and examination of it and its derivatives, no compound containing a benzene ring fused to an azulene has as yet been described. Cook, McGinnis, and Mitchell (*J.*, 1944, 286) have, however, recorded unsuccessful attempts to produce 5 : 6-benzazulene by dehydrogenation.

1 : 2-*Benzazulene* has now been synthesised by two methods. The first of these is an extension of an azulene synthesis which was designed to serve as a model not only for this preparation but also for that of heptalene (*bicyclo*[5 : 5 : 0]dodecahexaene) (II), through the use of *cyclo*heptanone as starting material.

(I.)   (II.)

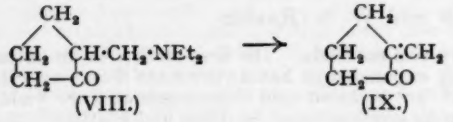
The Azulene Synthesis.—Two alternative methods for the preparation of the hexahydroindan-5-one (XV), required for the azulene synthesis, were explored. When the condensation of ethyl *cyclo*pentan-2-one-1-carboxylate (III) with 4-diethylaminobutan-2-one methiodide (IV) was carried out in ethanol solution at the boiling point, in the presence of sodium ethoxide, a neutral substance $C_{14}H_{24}O_5$ was isolated. This has been formulated as (VI):



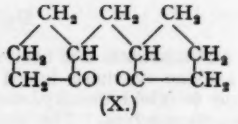
(III.) (IV.) (V.) (VI, R = Et.) (VII, R = H.)

The action of alcoholic alkali on this latter substance (VI) produced a liquid acid which, on the evidence of the saponification equivalent of its *diethyl* ester, was considered to be α-butan-3-onyladipic acid (VII). That the formation of (VI) occurred through the intermediate formation of (V) was indicated by the isolation of 2-*carbethoxy*-2-*butan*-3′-*onyl*cyclo*pentanone* (V) when the condensation was carried out in ethanol at 0°. This compound (V) was also produced when the reaction was carried out in an inert medium (benzene) but no conditions were found for its cyclisation and hydrolysis to (XIII). These results are similar to those obtained by Rapson (*J.*, 1936, 1626) by the reaction of ethyl *cyclo*pentan-2-one-1-carboxylate with αβ-unsaturated ketones. In the alternative and successful route the Mannich base from *cyclo*pentanone, formaldehyde, and morpholine was preferable to that from acetone, formaldehyde, and diethylamine. However, before morpholine was used, an attempt was made to prepare the Mannich base (VIII) from

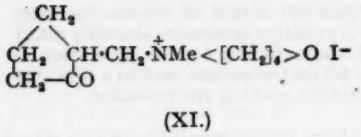
diethylamine. From the reaction between *cyclo*pentanone, diethylamine hydrochloride, and formaldehyde two substances were isolated. The first one, a low-boiling oil, had the formula, $C_9H_{16}O$, and has been formulated as 2-methylene*cyclo*pentanone (IX) since it gave 2-methyl-*cyclo*pentanone on hydrogenation in the presence of palladium–calcium carbonate catalyst. The second substance, a high-boiling, viscous oil was a diketone of the formula $C_{11}H_{16}O_2$, which is formulated as bis*cyclo*pentan-2-onylmethane (X). The formation of these substances is attributed to the instability of the Mannich base (VIII) which is presumably a first product under the conditions of reactions used. 2-Diethylamino*cyclo*pentanone (VIII) has been recorded subsequently to this work (Skoda, *Bull. Soc. chim.*, 1946, 328) but we have not had access to a description of the conditions used.



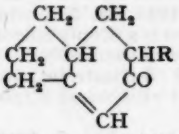
(VIII.) (IX.)



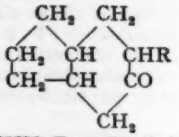
(X.)



(XI.)

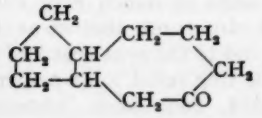


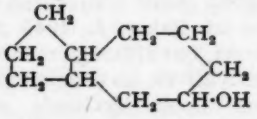
(XII, R = CO_2Et.)
(XIII, R = H.)



(XIV, R = CO_2Et.)
(XV, R = H.)

(XVI.)

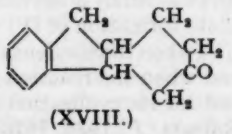




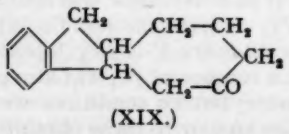
(XVII.)

The condensation between 2-(morpholinomethyl)*cyclo*pentanone methiodide (XI) and acetoacetic ester in anhydrous ethanol in the presence of sodium ethoxide proceeded smoothly to give a good yield of 6-*carbethoxy*-5 : 6 : 7 : 8-*tetrahydroindan*-5-*one* (XII) in two diastereoisomeric forms. Hydrogenation of the mixture gave 6-*carbethoxyhexahydroindan*-5-*one* (XIV, mixed isomers), hydrolysis of which was carried out by heating at 180—190° with glycerol, containing 10% of water (cf. du Feu, McQuillin, and Robinson, *J.*, 1937, 53), to give hexahydroindan-5-one (XV, mixed isomers) in moderate yield. The results obtained in the ring expansion of this substance with diazomethane accord with those reported by Plattner, Fürst, and Studer (*Helv. Chim. Acta*, 1947, **30**, 1091) some months after the present work was completed. No epoxide was isolated, but a mixture of the semicarbazones of the isomeric *bicyclo*[5 : 3 : 0]decan-3-ones (XVI) was formed directly from the reaction mixture, and was separated into its constituents. The reduction of the ketones derived from these semicarbazones to yield a stereoisomeric mixture of bicyclo[5 : 3 : 0]*decan*-3-*ols* (XVII) presented no difficulty. The dehydrogenation of this carbinol was carried out in a vacuum at 300—350° over a palladium–charcoal catalyst using an apparatus specially designed for this purpose. The intensely blue distillate was proved to be azulene by conversion into the known 2 : 4 : 6-trinitrotoluene derivative.

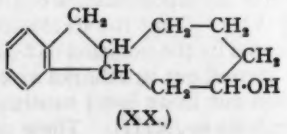
1 : 2-*Benzazulene*. *First Method*.—For the synthesis of 1 : 2-benzazulene, 1 : 2 : 3 : 4 : 10 : 11-hexahydrofluoren-3-one (XVIII) was prepared from indan-1-one by a *cyclo*hexenone synthesis (Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 284) and submitted to the action of diazomethane to give a mixture of ketones formulated as 9 : 10-benz*bicyclo*[5 : 3 : 0]-dec-9-en-3-one (XIX, mixed isomers) by analogy with the products of the reaction previously described. Neither the mixed semicarbazones nor the mixed oximes of this ketone could be



(XVIII.)



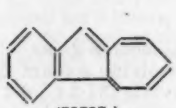
(XIX.)



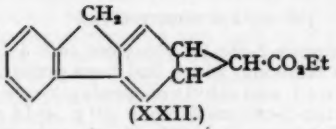
(XX.)

induced to crystallise, but the 2 : 4-*dinitrophenylhydrazones* crystallised well. The reduction of the ketone (XIX, mixed isomers) with sodium and ethanol, proceeded smoothly to give 9 : 10-*benz*bicyclo[5 : 3 : 0]*dec*-9-*en*-3-*ol* (XX, mixed isomers), which was an extremely viscous liquid. The value of the dehydrogenation apparatus previously mentioned is particularly clear

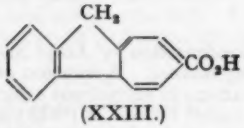
in this case. An attempt to dehydrogenate the carbinol (XX) by heating it with sulphur at 200—220° resulted in polymerisation. Heating with palladium–charcoal and passing over palladium–charcoal at 300—350° in the vapour phase were equally ineffective in promoting dehydrogenation. When, however, the previously mentioned vacuum-dehydrogenation technique was used, a comparatively high yield of 1 : 2-benzazulene (XXI) was realised. Whenever new catalyst was used in this dehydrogenation the first few drops of distillate consisted of a colourless crystalline substance (m. p. 94—97°). Investigation of this compound was not possible as only a very few milligrams were produced in all, but the m. p. indicated that it might have been phenanthrene (m. p. 99°) formed by rearrangement of 1 : 2-benzazulene



(XXI.)



(XXII.)



(XXIII.)

[cf. the rearrangement of azulene to naphthalene in a vacuum under the influence of heat (Heilbronner and Wieland, *Helv. Chim. Acta*, 1947, **30**, 947)]. Like other azulenes 1 : 2-benzazulene was found to be soluble in 85% phosphoric acid, from which it could be regenerated by

FIG. 1.

Ultra-violet absorption curves of 1 : 2-*benzazulene*(——) *and azulene* (·—·—).

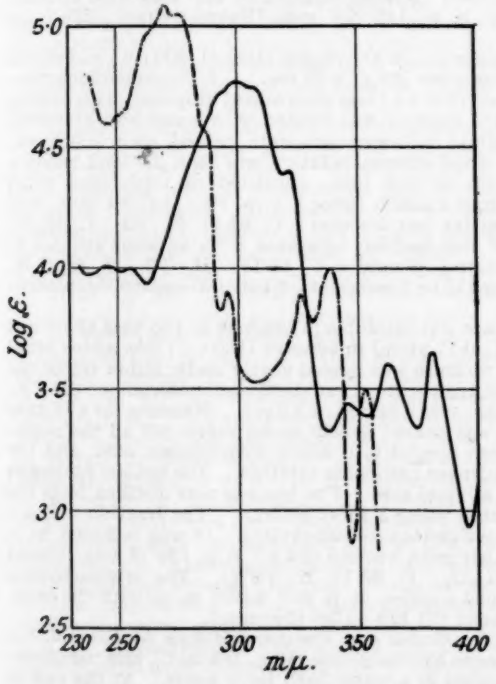
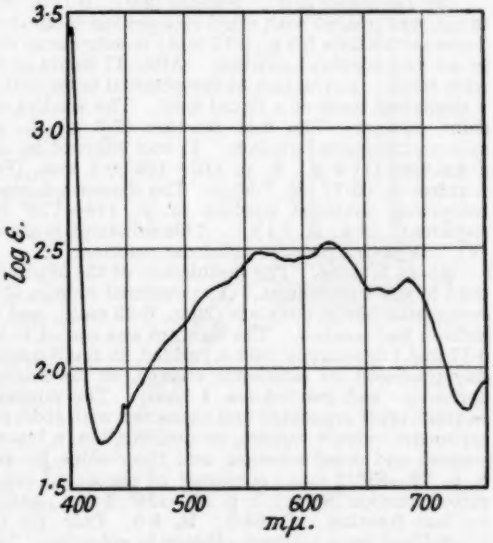


FIG. 2.

Visible absorption curve of 1 : 2-*benzazulene.*



the addition of ice-cold water. Making use of this property the azulene was extracted from the crude dehydrogenation product, that part of the reaction mixture insoluble in phosphoric acid being recycled through the apparatus to give more benzazulene. It formed well-defined, highly-crystalline and deeply-coloured *complexes* with both 2 : 4 : 6-trinitrotoluene and 1 : 3 : 5-trinitrobenzene. The pure hydrocarbon was obtained from either of these complexes by decomposing the complex on a column of alumina (cf. Plattner and St. Pfau, *Helv. Chim. Acta*, 1937, **20**, 224). The hydrocarbon crystallised from ethanol in deep green plates, which sublimed somewhat below the melting point and decomposed slowly on melting. In solution it exhibited an intense blue colour with a faint tinge of red at certain dilutions. The ultra-violet absorption spectrum (Fig. 1) shows a very marked resemblance to that of azulene which is given

in the same diagram. The visible absorption spectrum (Fig. 2) is typical of the azulenes, the absorption maxima being, in general, very broad bands.

1 : 2-*Benzazulene*. ***Second Method*** (with D. H. S. Horn).*—The reaction of diazoacetic ester with fluorene (cf. St. Pfau and Plattner, *Helv. Chim. Acta*, 1939, **22**, 202) gave a condensation product formulated as (XXII), hydrolysis of which yielded the acid (XXIII). When this acid was distilled in a vacuum over palladium–charcoal a high yield of 1 : 2-benzazulene was obtained. This synthesis is being exploited as a mode of access to 1 : 2-benzazulene and its derivatives in quantities sufficient for an examination of their chemical properties.

Experimental.

(M. p.s are uncorrected.)

*Condensation of Ethyl Sodiocyclo**pentan**-2-one-1-carboxylate with 4-Diethylaminobutan-2-one.*—(a) *In boiling ethanol.* A solution of sodium ethoxide, which had been prepared by dissolving sodium (3·9 g., 0·17 atom) in anhydrous ethanol (300 c.c.), and ethyl *cyclo*pentan-2-one-1-carboxylate (31·2 g., 0·2 mol.) was cooled in ice. 4-Diethylaminobutan-2-one methiodide (40 g., 0·14 mol.), prepared according to the method of du Feu, McQuillin, and Robinson (*J.*, 1937, 56), in anhydrous ethanol (120 c.c.) was then added dropwise. After one hour the solution was heated under reflux for 3 hours, cooled, and mixed with water and ether. The ether was evaporated from the dried, neutral extract, and the residue distilled giving unchanged ethyl *cyclo*pentanonecarboxylate (7·5 g.), b. p. 90—100°/0·1 mm., and a fraction (24 g.), b. p. 100—144°/0·1 mm. Redistillation of this latter fraction yielded an oil (15·4 g.), $n_D^{23\cdot5°}$ 1·4438, b. p. 143—149°/0·1 mm. (Found: C, 61·2, 61·8; H, 8·8, 8·8. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%). This substance which has been formulated as *diethyl α-butan-3-onyladipate* (VI) gave no ketonic reactions, but gave a positive iodoform reaction. This behaviour is in accordance with the behaviour of analogous compounds isolated by Rapson (*loc. cit.*). Saponification of this ester with alcoholic alkali yielded an acid which could not be induced to crystallise. Re-esterification of this acid with ethanol, containing a trace of sulphuric acid, gave an ester, b. p. 140°/0·1 mm. [Found: equiv., 138·7 (by saponification). Calc. for $C_{14}H_{24}O_5$: equiv., 136].

(b) *In ethanol at* 0°. Sodium (3·9 g., 0·17 atom), dissolved in anhydrous ethanol (300 c.c.) and cooled in ice, was treated with ethyl *cyclo*pentan-2-one-1-carboxylate (39 g., 0·25 mol.). 4-Diethylaminobutan-2-one methiodide (49 g., 0·17 mol.) in anhydrous ethanol (100 c.c.) was then added dropwise, with cooling in ice and constant swirling. After 17 hours at 0° the mixture was diluted with water and extracted with ether. Extraction of the ethereal layer with sodium hydrogen carbonate yielded, on acidification, a negligible trace of a liquid acid. The washed and dried ethereal solution was then distilled, using a short column. The first fraction (7·6 g.), b. p. 75—80°/0·1 mm., consisted of unchanged ethyl *cyclo*pentanonecarboxylate. It was followed by a mixed fraction (6·0 g.), b. p. 80—115°/0·1 mm., and a fraction (11·6 g.), b. p. 115—120°/0·1 mm. (Found for last fraction: C, 63·4; H, 7·9. $C_{12}H_{18}O_4$ requires C, 63·7; H, 7·9%). The *disemicarbazone* of this fraction separated from aqueous ethanol in colourless, flattened needles, m. p. 178—179° (decomp.) (Found: C, 49·15; H, 7·3. $C_{14}H_{24}O_4N_6$ requires C, 49·4; H, 7·1%). This substance is considered to be 2-*carbethoxy*-2-*butan*-3′-*onyl*cyclo*pentanone* (V). It gave a positive iodoform reaction.

(c) *In benzene.* The methiodide of the Mannich base was insoluble in benzene so the base alone was used in this experiment. To powdered sodium (3·9 g., 0·17 atom) in benzene (150 c.c.) was added ethyl *cyclo*pentanonecarboxylate (39 g., 0·25 mol.), and the mixture was heated gently under reflux till all the sodium had reacted. The mixture was cooled to room temperature and diethylaminobutanone (24·5 g., 0·17 mol.) in benzene (50 c.c.) added, in small quantities, over a period of 2 days. Standing for a further day produced no noticeable change, so the mixture was heated gently under reflux till all the sodio-derivative had reacted (*ca.* 1 hour). The mixture was poured into dilute hydrochloric acid, and the benzene layer separated and extracted with sodium hydrogen carbonate solution. The sodium hydrogen carbonate extract yielded, on acidification, a trace of a liquid acid. The benzene was distilled from the washed and dried solution, and the residue fractionated using a short column. The fraction (8·1 g.), b. p. 79—81°/2 mm., consisted of unreacted ethyl *cyclo*pentanonecarboxylate. It was followed by a mixed fraction (8·2 g.), b. p. 81—139°/3 mm., and a fairly pure fraction (6·4 g.), b. p. 139°/3 mm. (Found for last fraction: C, 64·9; H, 8·0. Calc. for $C_{12}H_{18}O_4$: C, 63·7; H, 7·9%). The semicarbazone crystallised from aqueous ethanol in colourless, flattened needles, m. p. and mixed m. p. with the semicarbazone of 2-carbethoxy-2-butan-3′-onyl*cyclo*pentanone (V) 178—179° (decomp.).

Reaction of cyclo*Pentanone with Diethylamine Hydrochloride and Paraformaldehyde in Ethanol.*—A solution of *cyclo*pentanone (34·5 g., 0·4 mol.), diethylamine hydrochloride (43 g., 0·4 mol.), and paraformaldehyde (12 g., 0·52 mol.) in ethanol (20 c.c.) was heated in a water-bath for 5 hours. At the end of this period the solution was cooled, diluted with water, basified with sodium hydroxide, and extracted with ether. The washed and dried ethereal extract yielded two fractions on distillation: fraction (i) (8 g.), b. p. 60—70°/18 mm., and fraction (ii) a viscous red oil (10 g.), b. p. 120—200°/2·5 mm. Redistillation of the first fraction gave a colourless oil, $n_D^{23°}$ 1·4665, b. p. 150—163°. The semicarbazone separated from ethanol in colourless rhombohedra, m. p. 214°, with softening and decomposition a few degrees below this temperature (Found: C, 54·9; H, 7·35. Calc. for $C_7H_{11}ON_3$: C, 54·8; H, 7·2%). Hydrogenation in methanol solution in the presence of palladium–calcium carbonate catalyst afforded a colourless oil (too small in quantity for accurate measurement of the boiling point). The semicarbazone crystallised in small colourless needles from ethanol, m. p. 167·5—168·5° (Found: C, 53·7. Calc. for $C_7H_{13}ON_3$: C, 54·2%).

* The same synthesis by Plattner, Fürst, Chopin, and Winteler (*Helv. Chim. Acta*, 1948, **31**, 501) came to our notice only after this work had been submitted for publication.

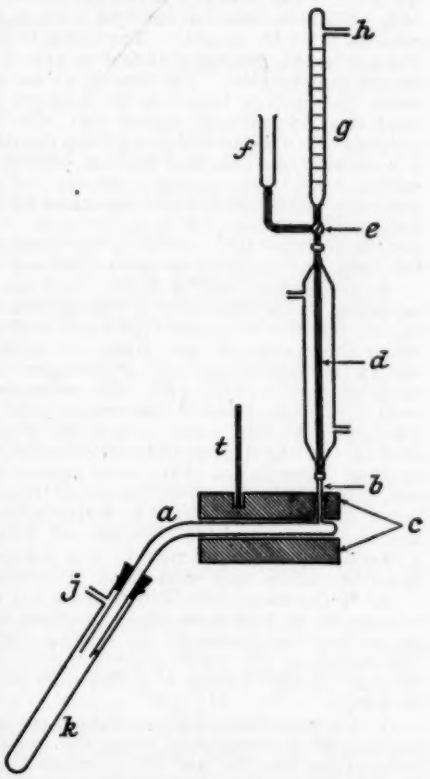
Fraction (ii) was redistilled giving a light yellow oil, b. p. 129—130°/0·1 mm., which contained no nitrogen (Found : C, 73·0, 73·4; H, 8·0, 8·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). This substance is considered to be *bis*cyclo*pentan*-2-*onylmethane* (X). The *disemicarbazone* formed minute, colourless crystals from ethanol, m. p. 227° (decomp.) (Found : C, 53·5; H, 7·6. $C_{13}H_{22}O_2N_6$ requires C, 53·0; H, 7·5%).

6-*Carbethoxy*-5 : 6 : 7 : 8-*tetrahydroindan*-5-*one* (XII).—The methiodide of 2-(morpholinomethyl)*cyclo*pentanone (Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, **72**, 233) was prepared by mixing the base (9·2 g., 0·05 mol.) and methyl iodide (8·5 g., 0·06 mol.) at room temperature. The mixture warmed spontaneously after a few minutes; it was then left for about half an hour and crystallised in short colourless needles which were washed with dry ether and dried in a vacuum.

Sodium (1·44 g., 0·063 atom), dissolved in a mixture of freshly-distilled ethyl acetoacetate (8·45 g., 0·065 mol.) and absolute ethanol (50 c.c.), was treated with 2-(morpholinomethyl)*cyclo*pentanone methiodide (16·2 g., 0·05 mol.) in absolute ethanol (100 c.c.), and the solution heated gently under reflux on a water-bath for 3 hours. The solution was then cooled, diluted with water, and ether extracted. Distillation of the dried neutral ethereal extract gave a first fraction (0·7 g.), b. p. 40—50°/0·5 mm., consisting of unchanged ethyl acetoacetate. The second fraction (4·9 g.), a yellow oil, b. p. 115—170°/1 mm., contained the desired *compound*. The fraction was redistilled, giving a pale yellow oil (2·7 g.), $n_D^{26°}$ 1·5079, b. p. 119—131°/0·5 mm. (Found : C, 69·0; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). On keeping it for 2 days a crop of crystals separated from this oil. Recrystallisation from light petroleum (b. p. 30—80°) gave colourless, prismatic needles, m. p. 74—75° (Found : C, 69·1; H, 7·6%). These two substances were regarded as stereoisomers.

FIG. 3.

Dehydrogenation apparatus.



6-*Carbethoxyhexahydroindan*-5-*one* (XIV).—6-Carbethoxy-5 : 6 : 7 : 8-tetrahydroindan-5-one in ethanol was hydrogenated in the presence of palladium–calcium carbonate catalyst [2% Pd, prepared according to Busch and Stöve (*Ber.*, 1916, **48**, 1063)] at 4 atmospheres, the theoretical amount of hydrogen being absorbed in 4 hours. The *hexahydroindanone* distilled as a colourless oil, $n_D^{25°}$ 1·4960, b. p. 113—118°/0·05 mm. (Found : C, 68·8; H, 8·5. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%).

Hexahydroindan-5-*one* (XV).—The above keto-ester (7·9 g.) was heated with glycerol (100 c.c.) and water (10 c.c.) at 180—190° for 4 hours. After dilution of the mixture with two volumes of water the product was isolated by ether extraction. Distillation of the dried neutral extract yielded a colourless oil (2·5 g.), b. p. 65—95°/1 mm. For analysis this was redistilled, $n_D^{27°}$ 1·4814, b. p. 110—114°/17 mm. (Found : C, 77·3; H, 9·9. Calc. for $C_9H_{14}O$: C, 78·2; H, 10·1%). The *semicarbazone* separated from ethanol or dilute acetic acid in colourless, feathery needles, m. p. 193—195·5° (decomp.) when heated at the rate of 1°/min., and m. p. 183—186° when heated at the rate of 0·5°/min. (Found : C, 61·9; H, 8·4. Calc. for $C_{10}H_{17}ON_3$: C, 61·5; H, 8·7%). Plattner, Fürst, and Studer (*loc. cit.*) give m. p. 187° for a stereoisomeric mixture of hexahydroindan-5-ones. Cook and Linstead (*J.*, 1934, 946) give m. p. 203° for the *cis*-isomer whilst Hückel and Goth (*Ber.*, 1934, **67**, 2104) give m. p. 208° for the same isomer.

bicyclo[5 : 3 : 0]*Decan*-3-*one* (XVI).—Hexahydroindan-5-one (2 g., 0·015 mol.) in a little absolute ether at 0° was treated with diazomethane (0·82 g., 0·02 mol.) in absolute ether (50 c.c.). Absolute methanol (15 c.c.) was then added. No evolution of nitrogen took place till the solution warmed to room temperature. After 24 hours the colour of the solution had noticeably decreased, and after 3 days hardly any colour remained. The ether and most of the methanol were removed under reduced pressure, and the semicarbazone formed from the residue. The semicarbazone (1·65 g.) crystallised in thick, short needles from ethanol, and after 6 recrystallisations had m. p. 158·5—159·5° (Found : C, 63·2; H, 9·1. Calc. for $C_{11}H_{19}ON_3$: C, 63·2; H, 9·1%). The mother liquors yielded on concentration another semicarbazone crystallising in small colourless needles, m. p. 145—149°, from ethanol (Found : C, 63·4; H, 9·1%). These derivatives are regarded as stereoisomers. The mixed semicarbazones (1 g.) were hydrolysed with 10% hydrochloric acid (20 c.c.) and the regenerated ketone taken up in ether. Distillation of the dried, neutral extract yielded 0·75 g., b. p. 118—122°/12 mm.

bicyclo[5 : 3 : 0]*Decan*-3-*ol* (XVII).—Sodium (1·5 g.) was added to the *bicyclo*[5 : 3 : 0]decan-3-one in absolute ethanol (20 c.c.), in small quantities, over a period of 5 minutes. The mixture was shaken occasionally until all the sodium had dissolved, after which water was added. The bicyclo[5 : 3 : 0]-*decan*-3-*ol* was extracted with ether. Distillation of the dried neutral extract afforded a colourless viscous oil (2·47 g.), $n_D^{15·5°}$ 1·4980, b. p. 120—127°/11—12 mm. (Found : C, 77·4; H, 11·8. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%).

Dehydrogenation of bicyclo[5 : 3 : 0]*Decan*-3-*ol*.*—The dehydrogenation apparatus is shown diagram-

* We are indebted to Mr. D. H. S. Horn for the design of the apparatus used in this experiment.

matically in Fig. 3. The catalyst chamber (*a*) was constructed from "Pyrex" glass of about 12 mm. internal diameter and provided with an inlet tube (*b*) of about 1 mm. internal diameter. The heating block (*c*) (shown in section in the diagram) consisted of two superposed copper blocks, each of which had a semicircular channel, which together formed a cylindrical channel to accommodate the catalyst chamber (*a*). In addition the top block had two circular holes which accommodated the inlet tube (*b*) and the thermometer (*t*). It had a length of 5 in. and a cross-section of 2 in. by 2 in. This large size made it possible to control the temperature to well within 5° at over 300°, when using an ordinary gas burner as the source of heat. A very fine capillary tube (*d*) 20 cm. long and about 0·15 mm. internal diameter, was attached to the tube (*b*) by means of pressure tubing. The tube (*d*) was surrounded by a water-jacket to keep the temperature of the liquid flowing through it constant. This precaution ensured that the liquid in the capillary tube was maintained at a constant viscosity which greatly facilitated the attainment of a steady flow. The top of the capillary tube was attached, by means of rubber tubing, to one arm of a three-way tap (*e*). One of the other arms was fused to a reservoir (*f*) and the remaining arm to a 2 c.c. graduated pipette (*g*). The top of the pipette was sealed off, and near the top a side arm (*h*) was attached. The tube (*h*) was connected, by means of pressure tubing, to a 50 c.c. gas burette, containing mercury. The side arm (*j*) of the receiver (*k*) was connected to a water pump, which maintained a constant vacuum in (*a*). Since the pressure in (*a*) was constant, the rate of flow of liquid through (*d*) could be controlled by adjusting the pressure on the liquid in (*g*). This was done by raising or lowering the level of the mercury in the gas burette. The catalyst chamber (*a*) was packed with a mixture of 30% palladium–charcoal catalyst (Linstead and Thomas, *J.*, 1940, 1130) and freshly-ignited long fibre asbestos (1 : 1 by weight). The liquid to be dehydrogenated was placed in (*f*). The catalyst chamber was evacuated, gradually at first so as not to displace the catalyst, and the heating block raised to the desired temperature. The pipette (*g*) was filled through the tap (*e*) and the liquid then allowed to flow down the capillary tube into the chamber (*a*) where it was vapourised. The optimum rate of flow for most dehydrogenations carried out was found to be about 0·01 c.c./min. Proceeding in this way *bicyclo*[5 : 3 : 0]decan-3-ol (0·5 g.) was dehydrogenated at 350°. The intensely blue product was distilled in a vacuum, the pale blue fraction, boiling up to 100°/16 mm., being rejected. The very intensely blue residue (0·2 g.) was warmed in ethanol (0·5 c.c.) with 2 : 4 : 6-trinitrotoluene (0·03 g.). The black-brown needles of the complex which separated on cooling were recrystallised from ethanol. Repeated recrystallisation did not raise the m. p. above 94—95°. Plattner and St. Pfau (*Helv. Chim. Acta*, 1937, **20**, 224) give m. p. 99·5—100° (corr.) for the trinitrotoluene complex with azulene. The amount of material at this stage was so small that an analysis was not possible.

9 : 10-*Benz*bicyclo[5 : 3 : 0]*dec-9-en-3-one* (XIX).—Hexahydrofluoren-3-one (3 g., 0·016 mol.) prepared according to the directions of Harradence and Lions (*loc. cit.*) in absolute ether (10 c.c.) was added to an ice-cold ethereal solution (34·5 c.c.) of diazomethane (containing 0·88 g., 0·021 mol., of diazomethane), which had previously been dried over sodium for 3 hours. When methanol (16·5 c.c.) was added there was an immediate evolution of nitrogen. After 2 hours at 0° the solution was allowed to warm up to room temperature (15—16°). The ether and methanol were removed in a vacuum after 3 days and the residue, in a little ethanol, was treated with excess of semicarbazide hydrochloride and potassium acetate. The semicarbazone, which would not crystallise, was washed by decantation with water and a little alcohol. It was then hydrolysed with 10% hydrochloric acid (30 c.c.) and the resulting ketone taken up in ether. Distillation of the dried neutral extract afforded a main fraction (1·70 g.), b. p. 138—154°/0·5 mm. Redistillation gave a viscous oil, b. p. 130—134°/0·1 mm. Both the oxime and the semicarbazone failed to crystallise. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in flattened, yellow needles, m. p. 194—195° (Found: C, 62·8; H, 5·5. $C_{20}H_{20}O_4N_4$ requires C, 63·2; H, 5·2%). The 2 : 4-dinitrophenylhydrazone of this ketone from another experiment had m. p. 162—164°. Both of these derivatives depressed the m. p. of hexahydrofluoren-3-one 2 : 4-dinitrophenylhydrazone.

9 : 10-*Benz*bicyclo[5 : 3 : 0]*dec-9-en-3-ol* (XX).—Sodium (0·5 g.) was added in small quantities to a solution of 9 : 10-benz*bicyclo*[5 : 3 : 0]dec-9-en-3-one (1·09 g.) in absolute ethanol (9 c.c.). When all the sodium had dissolved the solution was diluted with water, and the product isolated with ether. Distillation of the dried, neutral extract afforded the *alcohol* as a very viscous, practically colourless oil (0·71 g.), $n_D^{15\cdot5°}$ 1·5628, b. p. 125—130°/0·5 mm. (Found: C, 83·5; H, 8·4. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%).

1 : 2-*Benzazulene* (XXI).—Dehydrogenation of 9 : 10-benz*bicyclo*[5 : 3 : 0]-dec-9-en-3-ol (3·3 g.) was successfully accomplished using the apparatus and procedure previously described. The optimum temperature was 330° and the optimum rate of flow 0·01 c.c./min. The first few drops of distillate from the dehydrogenation solidified to a colourless crystalline substance, m. p. 94—97°. This may have been phenanthrene (m. p. 99°) formed by intramolecular rearrangement of 1 : 2-*benzazulene*. This colourless distillate was followed by an intensely blue, almost black distillate. The latter was taken up in light petroleum (b. p. 20—40°), and cooled in ice. The benzazulene was extracted from this solution by shaking with ice-cold 85% phosphoric acid (70 c.c.) in three separate portions. The phosphoric acid solution, deep yellow in colour, was shaken several times with ice-cold petroleum to remove any unchanged material. In order to liberate the benzazulene, this solution was poured slowly into a mixture of crushed ice (800 g.) and peroxide-free ether (1000 c.c.). Evaporation of the solvent from the dried, neutral ethereal solution afforded crude crystalline 1 : 2-benzazulene (1·01 g.). The combined petroleum extracts from the above were washed, dried, and the solvent evaporated, leaving a mobile oil (2·2 g.). This was recycled through the dehydrogenation apparatus to yield a further 0·3 g. of crude 1 : 2-benzazulene. The 1 : 3 : 5-*trinitrobenzene* derivative was formed by warming a mixture of 1 : 2-benzazulene (14 mg.), trinitrobenzene (16 mg.), and ethanol (3 c.c.) till solution occurred. On cooling, the complex separated as long black-brown needles which only required one recrystallisation, m. p. 152·5—153·5° (Found: C, 61·6; H, 3·6. $C_{20}H_{13}O_6N_3$ requires C, 61·4; H, 3·35%). The *complex* with 2 : 4 : 6-trinitrotoluene was formed in an analogous manner. It separated from ethanol in stout, flattened, dark brown needles, m. p. 105·5—106·5° (Found: C, 62·6; H, 4·1. $C_{21}H_{15}O_6N_3$ requires C, 62·2; H, 3·7%). The pure hydrocarbon was obtained by allowing the 2 : 4 : 6-trinitrotoluene derivative (200 mg.), in a 1 : 1 mixture (20 c.c.) of benzene and *cyclo*hexane, to flow down a column of

alumina (B.D.H. "Chromatographic Grade") 14 cm. in height and 1·4 cm. in diameter. The *benzazulene* was eluted from the column with pure *cyclo*hexane leaving the trinitrobenzene behind. Evaporation of the solvent and recrystallisation of the residue from ethanol gave deep green plates, m. p. 176—177° (decomp.) (Found: C, 94·7; H, 6·1. $C_{14}H_{10}$ requires C, 94·4; H, 5·6%).

The Action of Diazoacetic Ester on Fluorene.—Diazoacetic ester (7·5 g.) was added dropwise over a period of 5 hours to vigorously stirred fluorene (70 g.), kept at 130°. After cooling, the mixture was dissolved in the minimum of boiling ethanol to which was added potassium hydroxide (20 g.) in a little water. After heating under reflux for 2 hours, the solution was cooled, and the excess of fluorene filtered off. Most of the ethanol was distilled off, water was added, and the mixture was thoroughly extracted with ether to remove any fluorene. The aqueous solution was then acidified, and the acid collected in ether. Evaporation of the ether from the dried extract left a viscous green acid (6·6 g.) which contained a certain amount of nitrogenous polymerisation products of diazoacetic ester. This acid (2·3 g.) was mixed with palladium–charcoal (0·2 g.), and distilled (free flame) in a vacuum (15 mm.). The solid green distillate was taken up in light petroleum (b. p. 20—40°), and shaken with alkali to remove any acid. This solution was then dried, and the 1 : 2-benzazulene extracted with 85% phosphoric acid as previously described, giving 0·6 g. of crude 1 : 2-benzazulene. The 1 : 3 : 5-trinitrobenzene derivative had m. p. and mixed m. p. (with the product from the last synthesis) 150—153° (Found: C, 61·6; H, 3·6%).

Absorption Spectra.—The measurements of the absorption spectrum of 1 : 2-benzazulene were carried out in *cyclo*hexane solution using a Beckman Quartz spectrophotometer.

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179. *Constitution of Conessine. Part I.*

By ROBERT D. HAWORTH, JAMES MCKENNA, and NAZAR SINGH.

The oil, $C_{21}H_{30}$, obtained by the action of heat on conessine dihydriodide gave, on selenium dehydrogenation, the hydrocarbons, $C_{19}H_{18}$, m. p. 78—79°, and $C_{19}H_{16}$, m. p. 194—195°. The former is essentially 3′-*ethyl*cyclo*pentenophenanthrene*, which has been synthesised for comparison purposes; certain inconsistencies between the synthetic product and the hydrocarbon obtained from conessine are ascribed to the presence of small amounts of inseparable impurities in the latter.

Späth and Hromatka (*Ber.*, 1930, **63**, 126) degraded conessine by Hofmann and Emde processes to a crystalline lævorotatory hydrocarbon, $C_{21}H_{30}$, m. p. 74°, which was reduced catalytically to a hexahydro-derivative, $C_{21}H_{36}$, m. p. 56—58°. A repetition of these experiments has shown that the final reduction yields two isomeric hydrocarbons, one of which is identical with the product obtained by Späth and Hromatka, and the second, m. p. 84°, $[\alpha]_D^{18°}$ 15°, with 5-*allo*pregnane.

Conessine is, therefore, a steroid alkaloid, containing one ethylenic linkage, a dimethylamino-group, a cyclic methylimino-group, and probably a 5-*allo*pregnane structure, but the present experimental data are insufficient for a complete solution of the problem.

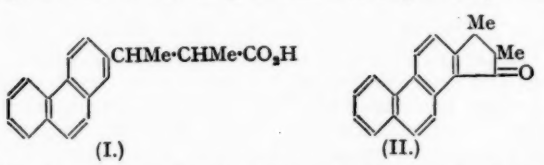
THE alkaloid conessine, $C_{24}H_{40}N_2$, has been isolated from the bark (Haines, *Trans. Med. Soc. Bombay*, 1858, **4**, 28) and seeds (Stenhouse, *Pharm. J.*, 1864, **5**, 493) of Indian "kurchi", *Holarrhena antidysenterica*, from the African species, *Holarrhena febrifuga* (Siddiqui, Misra, and Sharma, *J. Sci. Ind. Res., India*, 1945, **3**, 555), *Holarrhena Wulfsbergii* (Henry and Brown, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1923—1924, **17**, 381) and together with a subsidiary base, holarrhenine, $C_{24}H_{38}ON_2$, from *Holarrhena Congolensis* (Pyman, *J.*, 1919, **115**, 163). In addition to conessine a number of subsidiary bases have been isolated from extracts of "kurchi" bark and seeds. Ghosh and Ghosh (*J. Indian Chem. Soc.*, 1928, **5**, 477) and Ghosh and Bose (*Arch. Pharm.*, 1932, **270**, 100) isolated kurchine, $C_{23}H_{38}N_2$, and kurchicine, $C_{20}H_{36}ON_2$; Bertho, von Shuckmann, and Schonberger (*Ber.*, 1933, **66**, 786) obtained conessidine, $C_{21}H_{32}N_2$, conkurchine, $C_{21}H_{32}N_2$, and kurchenine, $C_{21}H_{32}O_2N_2$; Bertho (*Annalen*, 1944, **555**, 214) recorded the occurrence of conkurchenine, $C_{25}H_{34}N_2$: and Siddiqui and his collaborators (*J. Indian Chem. Soc.*, 1932, **9**, 553; 1934, **11**, 285; 787) separated conessimine, $C_{23}H_{38}N_2$, *iso*conessimine, $C_{23}H_{38}N_2$, conimine, $C_{22}H_{36}N_2$, conamine, $C_{22}H_{36}N_2$, conarrhimine, $C_{21}H_{34}N_2$, holarrhimine, $C_{21}H_{36}ON_2$, and holarrhine, $C_{20}H_{34}O_3N_2$.

The main alkaloid conessine is a ditertiary base containing a dimethylamino-group, a heterocyclic methylimino-group, and a double bond which is reduced with some difficulty. Many of the subsidiary oxygen-free alkaloids are *N*-demethylated conessines, and conessimine, *iso*conessimine, and conimine have been converted into conessine by methylation with formaldehyde and formic acid (Siddiqui, *J. Indian Chem. Soc.*, 1934, **11**, 283). Conkurchine gave conessine by partial reduction (2H) and *N*-methylation (Bertho, *loc. cit.*). Many of these bases have a pronounced tendency for molecular association and Bertho has suggested that kurchenine is a mixture of conessidine and conkurchine, and that kurchicine, conarrhimine, and *nor*conessine

(Haworth, *J.*, 1932, 631) are probably impure holarrhimine, conkurchine, and kurchine, respectively. No relationships have yet been established between the oxygen-containing bases, some of which, *e.g.* holarrhenine and holarrhimine, contain hydroxyl groups, and obviously the C_{20}-bases, kurchicine and holarrhine, cannot be formulated as *N*-demethylated conessines.

The application of Indian "kurchi" bark for the treatment of amoebic dysentery and tubercular affections in the indigenous medical practice has stimulated numerous investigations of the constituents of both Indian and African *Holarrhena* species, and pure conessine has been shown to possess interesting pharmacological properties. It has no anti-amoebic action *in vitro*, but *in vivo*, after intensive dosing, it showed marked activity (Jones, *Ann. Trop. Med. and Parasitol.*, 1946, **40**, 134; *Brit. J. Pharmacol.*, 1947, **2**, 217), and Meissner and Hesse (*Arch. exp. Path. Pharm.*, 1930, **147**, 339) have shown that it inhibits the growth of tubercle bacilli *in vitro*. In view of these interesting pharmacological properties, a knowledge of the chemical constitution of the alkaloid is very desirable. The results of Spath and Hromatka (*Ber.*, 1930, **63**, 126), which are outlined later (p. 834), indicate the presence of a tetracarbocyclic, system, but subsequent researches (Siddiqui and co-workers, *Proc. Indian Acad. Sci.*, 1935, **2**, 426; 1936, **4**, 283; 1939, **10**, 417; *J. Sci. Ind. Res., India*, 1945, **3**, 559; 1946, **7**, 435, 40; Bertho, *Annalen*, 1947, **557**, 200; 1947, **558**, 62; *Ber.*, 1947, **80**, 316) have added little to our knowledge of the ring system. We have been engaged for some time in a series of researches on the nature of conessine and related bases, and the present communication is concerned with the elucidation of the molecular framework of the alkaloids; the more detailed structural features will, it is hoped, be considered in later publications. The bases employed in these researches were isolated from the seeds of *Holarrhena antidysenterica*, a generous supply of which was kindly placed at the disposal of one of us some twenty years ago by Sir John Simonsen, F.R.S. Conessine was purified as the hydrogen oxalate, and a welcome additional yield was obtained by adopting Siddiqui's valuable procedure (*J. Indian Chem. Soc.*, 1934, **11**, 283) of methylating with formaldehyde the crude *nor*-bases which were present in the mother liquors. Important evidence concerning the constitution of conessine has been obtained from an examination of the crude hydrocarbon, "conessene," $C_{21}H_{30}$, which Siddiqui and Sharma (*Proc. Indian Acad. Sci.*, 1937, **6**, 191) prepared by pyrolysis of conessine dihydriodide. This hydrocarbon was dehydrogenated with selenium at 320°, and the products, after tedious systematic chromatography and fractional crystallisation, were resolved into (*a*) an oil with a purple fluorescence, (*b*) a *hydrocarbon*, m. p. 78—79°, and (*c*) a *hydrocarbon*, m. p. 194—195°. The fluorescent oil was partially dehydrogenated, and gave additional yields of the solid hydrocarbons, m. p. 78—79° and m. p. 194—195°, on further dehydrogenation. Most of our attention was, however, focussed on the hydrocarbon, m. p. 78—79°, which gave crystalline complexes with nitro-compounds (see table). The *trinitrobenzene* compound was most convenient for purification and characterisation purposes because of its stability. The *picrate* gradually decomposed in solution to give a *semi-picrate*, the *trinitrotoluene* derivative and *styphnate* were difficult to purify, and the 2 : 7-dinitroanthraquinone derivative dissociated very readily. Analysis and molecular-weight determinations on the hydrocarbon suggested the formula, $C_{19}H_{18}$, which was supported by analysis of the derivatives, and molecular-weight determinations of the picrate and semi-picrate by titration with dilute sodium hydroxide. The hydrocarbon, which was not oxidised to a quinone by chromic acid, gave a violet fluorescence in ultra-violet light, and as the absorption spectrum resembled closely that of Diels's hydrocarbon, a dimethyl- or ethyl-1 : 2-*cyclo*pentenophenanthrene structure was suspected, although the properties did not correspond with those of the five dimethyl derivatives reported in the literature. 2′ : 3′-Dimethyl- and 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene were therefore synthesised for comparison purposes.

1-2-Phenanthrylethyl bromide, prepared by Bachmann and Struve's method (*J. Org. Chem.*, 1940, **5**, 426), was condensed with diethyl methylsodiomalonate; the product, after hydrolysis and decarboxylation, gave two diastereoisomeric modifications of β-2-*phenanthryl*-α-*methylbutyric acid* (I), m. p. 144—146° and m. p. 121—123°, respectively. Cyclisation of the acid chlorides of



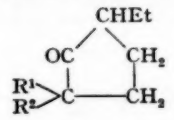
(I.) (II.) (III.)

either modification of (I) with aluminium chloride in nitrobenzene solution yielded 1′-*keto*-2′ : 3′-*dimethyl*-1 : 2-cyclo*pentenophenanthrene* (II). One modification of the ketone (II) was isolated

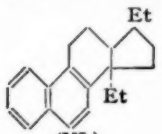
in a pure condition, m. p. 119—120°, and yielded on Clemmensen reduction *form* A, m. p. 119—120°, of 2′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene (III). The second modification of the ketone (II) was not purified; an impure sample, m. p. 99—102°, reduced by Clemmensen's method, yielded a mixture of form *A* and *form* B, m. p. 143—144°, of 2′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene (III).

The method used by Harper, Kon, and Ruzicka (*J.*, 1934, 124) for the preparation of Diels's hydrocarbon was adapted to the synthesis of 3′-*ethyl*-1 : 2-cyclo*pentenophenanthrene*. *Ethyl* 1-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate*, prepared by ethylation of ethyl *cyclo*pentan-2-one-1-carboxylate, was converted into *diethyl* α-*ethyladipate* (IV) by treatment with a small amount of sodium ethoxide. A Dieckmann reaction with sodium ethoxide in benzene on the ester (IV) yielded *ethyl* 3-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = H$; $R^2 = CO_2Et$), which on ethylation gave *ethyl* 1 : 3-*diethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = Et$; $R^2 = CO_2Et$). Ketonic hydrolysis of the ester (V; $R^1 = Et$; $R^2 = CO_2Et$) was very slow; repeated treatment with concentrated hydrochloric acid and regeneration from the *semicarbazone*, m. p. 195—196°, was necessary for the preparation of 2 : 5-*diethyl*cyclo*pentanone* (V; $R^1 = Et$; $R^2 = H$). Condensation of this ketone (V; $R^1 = Et$; $R^2 = H$) with the Grignard reagent of 2-α-naphthylethyl bromide, and dehydration of the resultant carbinol with phosphoric oxide gave the tetrahydro*cyclo*pentenophenanthrene (VI) which was not purified. Selenium dehydrogenation of the crude hydrocarbon (VI) gave a mixture which was separated by chromatography and fractional crystallisation into (*a*) an oil with a purple fluorescence, (*b*) 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII), (*c*) 1 : 4-di-α-naphthylbutane, m. p. 174°, and (*d*) a small amount

$EtO_2C{\cdot}CHEt{\cdot}[CH_2]_3{\cdot}CO_2Et$
(IV.)



(V.)



(VI.)

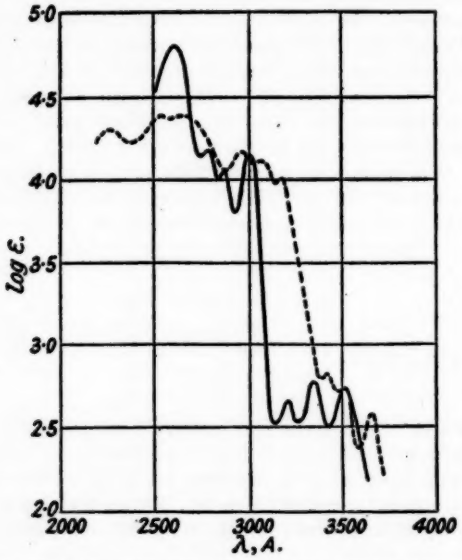
of a *hydrocarbon*, m. p. 194—195°. When the synthesis of 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII) was completed it was found that Riegel, Gold, and Kubico (*J. Amer. Chem. Soc.*, 1943, **65**, 1772) had prepared the hydrocarbon by a different method which did not involve selenium dehydrogenation, and we are deeply indebted to Dr. Riegel for specimens of his hydrocarbon, m. p. 84—85°, and the corresponding semi-picrate, m. p. 95—96°, which were identical with our preparations.

	Hydrocarbon "$C_{19}H_{18}$" from "conessine."	3′-Ethyl-1 : 2-*cyclo*-pentenophenanthrene.	Mixed m. p.	3′-Ethyl-1 : 2-*cyclo*-pentenophenanthrene + 5% of Diels's hydrocarbon.	2′ : 3′-Dimethyl-1 : 2-*cyclo*pentenophenanthrene. Form A.	Form B.
Hydrocarbon.....	78— 79°	84— 85°	78— 79°	78— 79°	119—120°	143—144°
Trinitrobenzene derivative	119—120	120—121	119—121	119—120	143—144	155—156
Semi-picrate	95— 96	95— 96	95— 96	95— 96	119—121	125—127
Picrate	95— 96	—	—	95— 96	—	—
Trinitrotoluene derivative	90— 91	94— 95	92— 93	93— 94	88— 90	96— 98
Styphnate	121—123	122—123	122—123	122—123	—	—
2 : 7-Dinitroanthraquinone derivative	234—235	234—236	234—236	234—235	—	—

The hydrocarbon, "$C_{19}H_{18}$," obtained from "conessene" was carefully compared with synthetic 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII) (see table). Although the two hydrocarbons differed by about 6° in melting point, mixtures had intermediate melting points and no depression in melting point was observed when the corresponding derivatives were mixed. The synthetic hydrocarbons however did not give the normal picrate. Our general conclusion from these results was that the hydrocarbon "$C_{19}H_{18}$," is essentially 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII), contaminated with small amounts of impurity, and it has been shown that a mixture of 3′-ethyl- and 3′-methyl-1 : 2-*cyclo*pentenophenanthrene containing about 5 per cent. of the latter, had m. p. 78—79°, was inseparable by chromatography or crystallisation, and gave a series of derivatives, including the normal picrate, m. p. 96°, indistinguishable from those given by the hydrocarbon, "$C_{19}H_{18}$." Furthermore, the behaviours of "conessene" and of the tetrahydro*cyclo*pentenophenanthrene (VI) during selenium dehydrogenation were

remarkably similar, and the hydrocarbons, m. p. 195—196°, produced in both cases were identical and gave identical *trinitrobenzene* derivatives, m. p. 138—139°. Owing to the small amounts available, it has not been possible to identify the hydrocarbon; the analytical results indicate the formula "$C_{19}H_{16}$," and the shift of the absorption spectra curve (see Fig.) as a whole to the higher wave-length may suggest the formation of an additional ring by loss of two hydrogen atoms from the hydrocarbon "$C_{19}H_{18}$" (see Ruzicka, Thomann, Brandenberger, Furter, and Goldberg, *Helv. Chim. Acta*, 1934, **17**, 200).

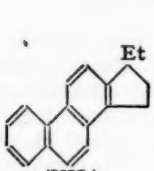
The natural and synthetic hydrocarbons, "$C_{19}H_{18}$," show no differences in ultra-violet absorption spectra, but as Diels's hydrocarbon and the two forms of 2′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene also gave identical curves (Fig.), the method is of little diagnostic value. There is, however, a serious and inexplicable discrepancy in the *X*-ray powder photographs of



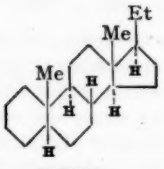
——— "$C_{19}H_{18}$", 3′-*ethyl*cyclo*pentenophenanthrene and* "cis" *and* "trans"-2′ : 3′-*dimethyl*cyclo*pentenophenanthrene.*
----- "$C_{19}H_{16}$".

"$C_{19}H_{18}$" and 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene which were kindly measured by Mr. D. K. Hill of the University Glass Technology Department, who reports that "the photographs show no exact resemblance apart from one line (d = 3·49 A.)."

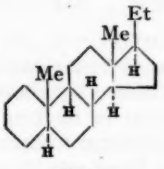
In spite of this inconsistency we remained convinced that "conessene" contained the 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene framework, and that the alkaloid conessine was a steroid base which should be convertible into pregnane (VIII), $C_{21}H_{36}$, or one of its stereoisomeric forms, of which four are recorded in the chemical literature. During their investigation on conessine, Spath and Hromatka (*loc. cit.*) converted the dimethiodide, by the action of silver oxide, into *apo*conessine, $C_{23}H_{35}N$ (see also Kanga, Azyar, and Simonsen, *J.*, 1926, 2123), the



(VII.)



(VIII.)



(IX.)

metho-salts of which did not undergo further Hofmann degradation. *apo*Conessine methochloride was, however, reduced by sodium amalgam to a strongly lævorotatory hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, which was reduced catalytically to a weakly dextrorotatory hexahydro-derivative, $C_{21}H_{36}$, m. p. 56—58°, $[\alpha]_D^{15°}$ 14·5° in benzene. This hexahydro-derivative, $C_{21}H_{36}$, does not correspond with pregnane or any of the known isomeric forms, but a repetition

of the work of Spath and Hromatka reveals the important fact that reduction of the lævorotatory hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, with a palladium–charcoal catalyst in acetic acid solution, yields about equal amounts of two stereoisomeric hexahydro-derivatives. One of these, m. p. 56—58°, $[\alpha]_D^{16°}$ 17° in chloroform, is obviously the form obtained by Spath and Hromatka, and the second isomer, which the previous workers failed to observe, had m. p. 84°, $[\alpha]_D^{15°}$ 15° in chloroform, and corresponded in properties with either 5-*allo*pregnane (IX) or pregnane (VIII). Samples of 5-*allo*pregnane and pregnane were therefore prepared from progesterone by conversion into 5-*allo*pregnane-3 : 20-dione and pregnane-3 : 20-dione by a modification of the method of Butenandt and Fleischer (*Ber.*, 1935, **68**, 2096), and the diones were reduced to the corresponding hydrocarbons by Clemmensen's method. 5-*allo*Pregnane and pregnane melted at 83—84° and 80—81°, respectively; no depression in m. p. was observed with mixtures of 5-*allo*pregnane and the hexahydro-derivative, m. p. 84°, but a large depression was obtained with pregnane. We are again indebted to Mr. D. K. Hill for the *X*-ray powder photographs which establish the identity of the hexahydro-derivative, m. p. 84°, and 5-*allo*pregnane.

Reduction of the hydrocarbon $C_{21}H_{30}$ has given a mixture of *allo*pregnane and an isomer, not identical with pregnane. A Δ^5-pregnene structure is considered unlikely for the alkaloid, as this should lead to a mixture of pregnane and 5-*allo*pregnane, or alternatively to a larger number of isomers.

These experiments have, therefore, accounted for all the carbon atoms of the conessine molecule, and the remaining problem of assembling a dimethylamino-group, a methylimino-group, and a double bond into the 5-*allo*pregnane (IX) framework will be discussed in later communications.

Experimental.

Isolation of Conessine.—Seeds (12 lbs.) of *Holarrhena antidysenterica* were crushed, passed through a 10-mesh sieve, mixed thoroughly with lime (2 lbs.), and extracted for 48 hours with alcohol (11 l.) in a tinned-copper Soxhlet apparatus. The extract was concentrated to a thick syrup, dissolved in chloroform, and bases removed in dilute hydrochloric acid. The acid extract was made alkaline with ammonia, and the bases (71 g.), isolated with ether, were mixed with a hot solution of oxalic acid (70 g.) in alcohol (250 c.c.). On cooling, conessine hydrogen oxalate (51 g.), m. p. 260° (decomp.), separated in colourless prisms. The filtrate was concentrated, diluted with water, and made alkaline with ammonia, and the recovered bases (30 g.), isolated with ether, were *N*-methylated by heating under reflux for 2 hours with 90% formic acid (15 c.c.), 36% formaldehyde (20 c.c.), and water (40 c.c.). Concentrated hydrochloric acid (20 c.c.) was added, and the solution concentrated to one half of its volume, diluted with water, and neutral impurities removed in chloroform. The acid liquors were made alkaline, and the recovered bases converted into hydrogen oxalate (18 g.), m. p. 260—262°, as described above.

The conessine hydrogen oxalate (69 g.), decomposed with sodium hydroxide, yielded the base which was distilled at 0·1 mm. (oil-bath temp. 220°) and crystallised from acetone in plates (30 g.), m. p. 125—126°.

" Conessene ".—Dry conessine dihydriodide [(25 g.) prepared from a dilute hydrochloric acid solution of conessine (15 g.) and a concentrated solution of potassium iodide (15 g.)] was covered with glass wool and heated in a distillation flask (500 c.c.) in a slow stream of hydrogen. When decomposition was complete, the oily contents of the flask and receiver were taken up in chloroform, diluted with an equal volume of ether, decanted from gum, washed with dilute hydrochloric acid, and dried, and the solvent removed, and the residue distilled at 0·1 mm. " Conessene " (6·5 g.), b. p. 165—170°/0·1 mm., had $[\alpha]_D^{18°}$ 32° in 1% alcoholic solution (Siddiqui and Sharma, *loc. cit.*, give $[\alpha]_D^{31°}$ 35°).

Selenium Dehydrogenation of " Conessene ".—" Conessene " (23 g.) and selenium (48 g.) were heated at 320—325° for 48 hours, and the product isolated first with chloroform and then with ether. Removal of the ether gave a pale yellow oil (23 g.) with a violet fluorescence, which was dissolved in light petroleum (b. p. 60—80°) (100 c.c.), and adsorbed on a column of alumina (25 cm. × 2 cm.). Successive elutions were made with (1) light petroleum (10 portions of 25 c.c.; b. p. 60—80°), (2) light petroleum containing 5% benzene (4 portions of 25 c.c.), (3) light petroleum containing 10 per cent. benzene (2 portions of 25 c.c.), (4) light petroleum and 20% benzene (1 portion of 25 c.c.), and the adsorption and elutions were repeated systematically until the product was separated into (*a*) an oil (10 g.), (*b*) a solid (10 g.), m. p. 52—100°, and (*c*) a solid (0·9 g.), m. p. 110—180°.

After a prolonged fractional crystallisation from alcohol, the solid, m. p. 52—100°, gave the hydrocarbon " $C_{19}H_{18}$ " (2·5 g.), m. p. 76—77°, raised to 78—79° by decomposing the trinitrobenzene complex (see below) by allowing its solution in light petroleum containing 5% of benzene to percolate through a column of alumina, when the trinitrobenzene was retained. The purified *hydrocarbon* crystallised from alcohol in colourless leaflets, m. p. 78—79° [Found : C, 92·7, 92·7, 92·9; H, 7·3; *M* (Rast), 235, 240; *M* (cryoscopic in benzene), 242; *M* (cryoscopic in *cyclo*hexane), 243. $C_{19}H_{18}$ requires C, 92·7; H, 7·3%; *M*, 246]. The hydrocarbon, which was optically inactive, could not be purified further by chromatographic adsorption, by distribution between light petroleum and methanol, or by recrystallisation. On long standing in the air, or when boiled in alcohol, the hydrocarbon suffered slight decomposition, and the pale yellow higher-melting impurities were easily removable by adsorption on alumina. Catalytic reduction proceeded very slowly in alcoholic solution in the presence of platinic oxide, and yielded a *tetrahydro*-derivative, b. p. 140—145°/0·05 mm. (Found : C, 91·2; H, 8·6. $C_{19}H_{22}$ requires C, 91·2; H, 8·8%), which was reconverted to the hydrocarbon, " $C_{19}H_{18}$," by dehydrogenation

with selenium. The *trinitrobenzene* derivative separated from methanol in long, flat, brownish-orange needles, m. p. 119—120° (Found: C, 65·4, 65·5, 65·4; H, 4·5, 4·6, 4·5; N, 9·2. $C_{25}H_{25}O_6N_3$ requires C, 65·4; H, 4·6; N, 9·2%). The normal *picrate*, prepared from the hydrocarbon (0·1 g.) and picric acid (0·15 g.) in methanol (2 c.c.), separated in long orange-yellow needles, m. p. 95—96° (Found: N, 8·6; *M*, 489. $C_{25}H_{21}O_7N_3$ requires N, 8·8%; *M*, 475), slowly changed in solution to the *semipicrate*, dark-red microscopic crystals, m. p. 96° [Found: C, 73·2; H, 5·3; N, 6·1; *M* (titration), 722. $C_{44}H_{30}O_7N_3$ requires C, 73·0; H, 5·4; N, 5·8%; *M*, 721] from alcohol–ether. This was also prepared directly from the hydrocarbon and less than the equivalent amount of picric acid. The *trinitrotoluene* derivative separated from methanol in pale yellow needles, m. p. 90—91° (Found: C, 65·5; H, 5·1; N, 8·7. $C_{26}H_{23}O_6N_3$ requires C, 66·0; H, 5·0; N, 8·9%); the *styphnate* crystallised from methanol in small needles, m. p. 121—123° (Found: N, 8·4. $C_{25}H_{21}O_8N_3$ requires N, 8·1%); and the 2 : 7-dinitroanthraquinone derivative crystallised from benzene–alcohol in red needles, m. p. 234—236°.

The fraction (*c*), m. p. 110—180°, from the dehydrogenation with selenium, was fractionally crystallised from alcohol. The *hydrocarbon* "$C_{19}H_{16}$" separated as colourless needles (30 mg.), m. p. 195—196° [Found: C, 92·9; H, 6·6; *M* (Rast), 249. $C_{19}H_{16}$ requires C, 93·4; H, 6·6%; *M*, 244]. The *trinitrobenzene* derivative crystallised from ethanol in orange-red needles, m. p. 138—139° (Found: C, 64·9; H, 3·9. $C_{25}H_{19}O_6N_3$ requires C, 65·6; H, 4·2%).

Synthesis of 3′-*Ethyl*-1 : 2-cyclo*pentenophenanthrene*.—*Ethyl* 1-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate*. Diethyl adipate was prepared in 95% yield, as described in *Org. Synth.*, Coll. Vol. II, p. 264, and converted in 85% yield into ethyl *cyclo*pentan-2-one-1-carboxylate by the method of Linstead and Meade (*J.*, 1934, 940). Granulated sodium (23·5 g.) and ethyl *cyclo*pentan-2-one-1-carboxylate (174 g.) were refluxed in benzene (400 c.c.) for 3 hours; ethyl iodide (200 g.) was added to the sodio-derivative, which separated as a thick cake, and the mixture heated under reflux for 10 hours. A further addition of sodium (2 g.) and ethyl iodide (20 g.) was made, and the heating continued for another 7 hours. The benzene layer was washed successively with water and dilute sodium hydroxide, dried, and distilled. *Ethyl* 1-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (144 g.), b. p. 120—122°/16 mm. (Found: C, 65·1; H, 8·5. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%), was obtained, which gave a negative ferric test.

Diethyl α-ethyladipate (IV). The above ester (92 g.) was heated with a solution of sodium (2·3 g.) in absolute alcohol (250 c.c.) for 12 hours, and after dilution with water (1500 c.c.) the product was extracted with ether, dried, and distilled. *Diethyl α-ethyladipate* (IV) (92 g.), b. p. 139—140°/12 mm. (Found: C, 62·6; H, 9·4. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%), was obtained.

Ethyl 3-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = H$; $R^2 = CO_2Et$). Diethyl α-ethyladipate (92 g.) was heated on the water-bath for 18 hours with pulverised sodium (13·8 g.), benzene (400 c.c.), and alcohol (1 c.c.). After decomposition with ice-cold 10% acetic acid (400 c.c.) the benzene layer was separated, dried, and distilled. *Ethyl* 3-*ethyl*cyclo*pentanone*-1-*carboxylate* (45 g.), b. p. 127—130°/18 mm. (Found: C, 65·2; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%), was obtained, and gave a strong blue colour with ferric chloride.

Ethyl 1 : 3-*diethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = Et$; $R^2 = CO_2Et$). The above ester (63 g.) was heated with sodium (8 g.) in benzene (400 c.c.) for 1 hour, and ethyl iodide (60 g.) was then added to the cake of sodio-compound. After 3 hours at room temperature, the mixture was heated under reflux overnight, and decomposed by the addition of water. The benzene layer was washed with dilute sodium hydroxide solution, dried, and distilled. *Ethyl* 1 : 3-*diethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (55 g.), b. p. 128—130°/13 mm. (Found: C, 67·7; H, 9·5. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%), was obtained.

2 : 5-*Diethyl*cyclo*pentanone* (V; $R^1 = Et$; $R^2 = H$). The above ester (32 g.) was heated under reflux for 12 hours with concentrated hydrochloric acid (65 c.c.). The mixture was diluted with water and extracted with ether, the extract washed with dilute sodium hydroxide and dried, the solvent removed, and the residual oil distilled. The fraction, b. p. 175—195°, was collected, and heated in methyl-alcoholic solution (150 c.c.) for 1½ hours with semicarbazide hydrochloride (32 g.) and sodium acetate (30 g.). The *semicarbazone*, precipitated by water and crystallised twice from methyl alcohol, was obtained as colourless prisms (12 g.), m. p. 195—196° (Found: C, 60·9; H, 9·6; N, 21·3. $C_{10}H_{19}ON_3$ requires C, 60·8; H, 9·4; N, 21·3%).

The unchanged keto-ester (V; $R^1 = Et$; $R^2 = CO_2Et$) was recovered from the mother liquors and the hydrolysis repeated.

2 : 5-*Diethyl*cyclo*pentanone*, recovered from the semicarbazone (11 g.) by heating with 15% hydrochloric acid (300 c.c.) for 1 hour, was isolated with ether and distilled; an oil (7 g.), b. p. 182°, was obtained (Found: C, 77·1; H, 11·3. $C_9H_{16}O$ requires C, 77·1; H, 11·4%).

3′-*Ethyl*-1 : 2-cyclo*pentenophenanthrene* (VII). The Grignard reagent prepared from 2-α-naphthylethyl bromide (15 g.), and magnesium (1·4 g.) in ether (90 c.c.) was added to a solution of 2 : 5-diethyl*cyclo*pentanone (7 g.) in benzene (50 c.c.). After being boiled for 1 hour, the mixture was left for 12 hours, and the ether removed on the water-bath and benzene (50 c.c.) added. The benzene solution was heated under reflux for 5 hours, the benzene was then removed, and the red, oily residue decomposed by the addition of 10% acetic acid (100 c.c.). The product, isolated with ether, was distilled, and the fraction (8·5 g.), b. p. 160—200°/0·2 mm., was collected and heated at 15 mm. pressure with phosphoric oxide (15 g.) at 140—150° for 1 hour. The mixture was cooled and decomposed with ice, and the dehydrated product isolated with ether, and distilled. The oil (7·0 g.), b. p. 180—190°/0·2 mm., was heated with selenium (15 g.) at 320—330° for 24 hours, and the product was extracted with chloroform, the solvent removed, and the residue taken up in light petroleum (b. p. 40—60°), and distilled over sodium. The fraction (6·0 g.) distilling at 160—200°/0·4 mm. was dissolved in light petroleum (b. p. 40—60°) (100 c.c.), adsorbed upon a column of alumina (30 × 2 cm.), and eluted first with 10 successive quantities (each 25 c.c.) of light petroleum (b. p. 40—60°), then with 3 similar washings containing 10% of benzene, and finally with 7 washings with benzene. Of the 20 fractions collected, the first 3 yielded an oil with a characteristic purple fluorescence.

The next 6 fractions were crystallised from methyl alcohol and yielded 3′-*ethyl*-1 : 2-cyclo*penteno*-*phenanthrene* (1·3 g.) as flat needles (not leaflets), m. p. 84—85° (Found: C, 92·7; H, 7·3. $C_{19}H_{18}$

requires C, 92·7; H, 7·3%), after chromatography of the trinitrobenzene complex, m. p. 120—121°. The semipicrate, m. p. 95—96°, styphnate, m. p. 120—122°, trinitrotoluene derivative, m. p. 94—95°, gave correct analytical figures and were identical with the derivatives described on p. 833 (see table). The 2 : 7-dinitroanthraquinone derivative, m. p. 234—236°, was also prepared.

The next 7 fractions gave 1 : 4-di-α-naphthylbutane (0·2 g.), as needles, m. p. 100—102°, from alcohol (Found : C, 92·6; H, 7·3. Calc. for $C_{24}H_{22}$: C, 92·8; H, 7·2), which gave a yellow dipicrate, m. p. 174° (Harper, Kon, and Ruzicka, *J.*, 1934, 127, gave m. p. 174°).

The last four fractions, crystallised from methanol, gave the hydrocarbon, "$C_{19}H_{16}$," m. p. 194—195° (Found : C, 92·9; H, 6·5) (trinitrobenzene derivative, m. p. 138—139°) identical with the hydrocarbon described on p. 836.

Synthesis of 2′ : 3′-*Dimethyl*-1 : 2-cyclo*pentenophenanthrene.*—*β-2-Phenanthryl-α-methylbutyric acids* (I). To a solution of diethyl methylsodiomalonate prepared from sodium (0·48 g.), diethyl methylmalonate (4·2 c.c.), and alcohol (20 c.c.) was added 1-2-phenanthrylethyl bromide (4·0 g.) in benzene (30 c.c.). After 12 hours at room temperature, the mixture was refluxed for 2 hours, the alcohol removed, and benzene and dilute hydrochloric acid added. The benzene was removed, and the residue heated at 100° for 1 hour with excess of 45% potassium hydroxide solution. After dilution and acidification the dicarboxylic acid was isolated with ether, and heated at 180° for ½ hour. Crystallisation from chloroform–light petroleum gave the mixture of *β-2-phenanthryl-α-methylbutyric acids* (I) (2·0 g.), m. p. 110—130°, which was separated by fractional crystallisation from *cyclo*hexane into *form* A, needles, m. p. 144—146° (Found : C, 82·2; H, 6·8. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%), and *form* B, small needles, m. p. 121—123° (Found : C, 82·1; H, 6·8%).

1′-*Keto*-2′ : 3′-*dimethyl*-1 : 2-cyclo*pentenophenanthrene* (II). The acid chloride, prepared from the mixture (6 g.), m. p. 110—130°, of the acid (I) and thionyl chloride (6 c.c.) in ether (60 c.c.) containing pyridine (2 drops), was dissolved in nitrobenzene (25 c.c.), and added dropwise to a solution of aluminium chloride (4·5 g.) in nitrobenzene (50 c.c.). After stirring for 12 hours at room temperature and for 2 hours at 80°, the mixture was decomposed with ice and hydrochloric acid, and the nitrobenzene removed. The product, isolated with benzene and decolourised with charcoal, was separated by repeated crystallisation from methyl alcohol and methyl alcohol–acetone (2 : 1) into *form* A of the ketone (II) which separated as prisms (0·9 g.), m. p. 119—120° (Found: C, 87·7; H, 6·2. $C_{19}H_{16}O$ required C, 87·7; H, 6·2%), and a mixture *B*, crystallising in plates (2·7 g.), m. p. 99—101° (Found : C, 87·6; H, 6·3%), and which yielded a mixture of hydrocarbons on reduction.

2′ : 3′-*Dimethyl*-1 : 2-cyclo*pentenophenanthrene* (III). *Form* A. Form *A* of ketone (II) (0·9 g.) was reduced by Clemmensen's method using amalgamated zinc (10 g.), toluene (5 c.c.), glacial acetic acid (20 c.c.), and concentrated hydrochloric acid (12 c.c.); a mixture of glacial acetic acid (12 c.c.) and concentrated hydrochloric acid (8 c.c.) was gradually added during the reduction. The product, isolated with ether, crystallised from methanol in platelets (0·75 g.), m. p. 119—120° (Found : C, 92·7; H, 7·3. $C_{19}H_{18}$ requires C, 92·7; H, 7·3%). The *trinitrobenzene* derivative crystallised from methanol in yellow needles, m. p. 143—144° (Found : C, 65·4; H, 4·4; N, 9·3. $C_{25}H_{21}O_6N_3$ requires C, 65·4; H, 4·6; N, 9·2%). The *picrate* crystallised from methanol in golden-red needles, m. p. 119—121° (Found : C, 62·7; H, 4·1; N, 8·4. $C_{25}H_{21}O_7N_3$ requires C, 63·2; H, 4·4; N, 8·8%).

2′ : 3′-*Dimethyl*-1 : 2-cyclo*pentenophenanthrene. Form* B. The mixture *B* of ketone (II) (1·7 g.), m. p. 99—102°, reduced similarly, yielded a mixture which, on fractional crystallisation from methanol, gave form *A*, described above, and *form* B of (III). The latter was obtained as plates (1 g.), m. p. 143—144° (Found : C, 92·7; H, 7·2%). The *trinitrobenzene* derivative crystallised from methanol in yellow needles, m. p. 155—156° (Found : C, 65·2; H, 4·6; N, 9·4%). The *picrate*, golden-red prisms from methanol, had m. p. 125—127° (Found : C, 52·7; H, 3·4; N, 11·5%).

Hydrogenation of the Unsaturated Hydrocarbon $C_{21}H_{30}$.—The unsaturated hydrocarbon (0·20 g.) [prepared as described by Spath and Hromatka (*loc. cit.*)] in glacial acetic acid (20 c.c.) was shaken in a hydrogen atomsphere with 8% palladium–charcoal (0·20 g.). The hydrogenation, which was very rapid at first, was complete in a few hours (total uptake at 12° and 753 mm., 55 c.c.; calculated for 6H, 50 c.c.). Shaking was continued overnight, and the mixture then warmed and filtered, and the catalyst washed with hot glacial acetic acid (10 c.c.). On being kept, the combined filtrate and washings slowly deposited white flakes (80 mg.; m. p. 75—80°), which after several recrystallisations from methanol gave the *hydrocarbon*, $C_{21}H_{36}$, as rectangular prisms, m. p. 83—84°, saturated to bromine and to a cold acetone solution of potassium permanganate (Found : C, 87·0; H, 12·3. $C_{21}H_{36}$ requires C, 87·4; H, 12·6%). $[\alpha]_D^{20°}$ + 15° (in chloroform : *c*, 0·3). Mixtures with the unsaturated hydrocarbon, m. p. 74—76°, and with pregnane, m. p. 80—81°, melted at 55—60° and 50—55° respectively, but no depression in m. p. was observed in admixture with 5-*allopregnane*, m. p. 83—84°.

The acetic acid mother-liquors were evaporated to dryness under reduced pressure, and the residue dissolved in absolute ether (15 c.c.) and filtered through a column of activated alumina (8 × 1 cm.). The filtrate was evaporated, and the residue recrystallised from methanol, giving rectangular plates (70 mg.), m. p. 56—58°, unchanged on further recrystallisation (Found: C, 87·2; H, 12·1%); $[\alpha]_D^{20°}$ + 17° (in chloroform : *c*, 0·25). Spath and Hromatka (*loc. cit.*) give m. p. 56—58° and $[\alpha]_D^{15°}$ + 14·5° (in benzene : *c*, 7·5).

5-allo*Pregnane*-3 : 20-*dione* and *Pregnane*-3 : 20-*dione from Progesterone.*—Progesterone (0·238 g.) dissolved in glacial acetic acid (20 c.c.) was shaken with Adams's catalyst (0·025 g.) in a hydrogen atmosphere. Hydrogenation was complete in 20 minutes (uptake at 19° and 740 mm., 66 c.c.; calculated for 6H and catalyst, 62 c.c.). After being shaken for one hour the catalyst was removed, the filtrate evaporated under reduced pressure, and the residue heated under reflux for five minutes with methanol (20 c.c.) containing potassium hydroxide (0·5 g.), and the solution neutralised with carbon dioxide, and evaporated. The residue was treated with ether and water, the ether removed, and the resulting mixture of pregnane- and 5-*allo*pregnane-diols was oxidised by treatment with a solution of chromic anhydride (0·240 g.) in glacial acetic acid (20 c.c.). After being left overnight, the solvent was removed under reduced pressure at 30°, and the residue taken up in ether, washed first with dilute sulphuric acid and then with sodium carbonate solution, and evaporated. The residue, crystallised thrice from acetone–

ether (1 : 1), gave pure 5-*allo*pregnanedione (50 mg.), m. p. 201—203° (literature, 199°; 200·5°). After the separation of a further crop of 5-*allo*pregnanedione the mother liquors were evaporated, the residue distilled at 0·0001 mm., and the first portion of the distillate, on crystallisation from dilute methanol, gave pregnanedione (11 mg.), m. p. 115—117° (literature, 119°; 123°).

5-allo*Pregnane and Pregnane.*—A solution of 5-*allo*pregnanedione (50 mg.) in glacial acetic acid (5 c.c.) was heated under reflux for 2½ hours with concentrated hydrochloric acid (5 c.c.) and amalgamated zinc (2 g.). The hydrocarbon, isolated with light petroleum, was dissolved in dry light petroleum (b. p. 40—60°, 2 c.c.), the solution poured on to an alumina column (18 × 1 cm.), and eluted with the same solvent. The first fraction (2 c.c.) from the column gave a semi-solid residue, and the second fraction (2 c.c.) on evaporation yielded a residue which solidified immediately, and, after two recrystallisations from acetone, gave 5-*allo*pregnane as colourless rectangular prisms, m. p. 83—84°.

Pregnane, m. p. 80—81° (from methanol), was prepared by a similar method from pregnanedione.

Our thanks are due to the British Schering Research Institute for a generous gift of chemicals, to Imperial Chemical Industries Limited for grants for the purchase of materials, to the University Research Fund for a grant for the purchase of an extraction apparatus, and to the Indian Government for a maintenance grant to one of us.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, May 10th,* 1948.]

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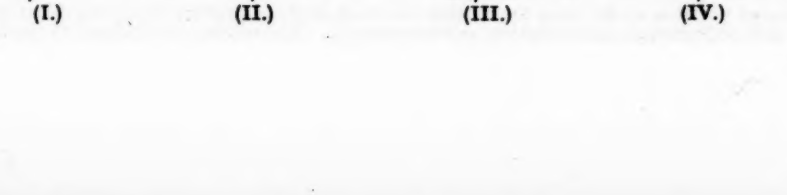
180. *The Structure of γ-Curcumene.*

By R. D. BATT and S. N. SLATER.

The structure of (+)-γ-curcumene, the main sesquiterpene component of the essential oil of *Libocedrus bidwillii*, Hook, has been investigated. Of the possible formulæ considered, (III) is regarded as the most satisfactory representation.

THE essential oil of *Libocedrus bidwillii*, Hook, a coniferous tree endemic to New Zealand, has been examined by Goudie (*J. Soc. Chem. Ind.*, 1923, **42**, 350T) and by Birrell (*ibid.*, 1932, **51**, 398T). Goudie made a preliminary study of a dextrorotatory sesquiterpene fraction which was more fully examined by Birrell. Recently, a precise fractionation of this oil has been completed (Batt and Hassall, to be published elsewhere), and this communication deals with an investigation into the structure of the purified main sesquiterpene component, to which the name (+)-*γ-curcumene* is assigned.

The analysis of the sesquiterpene confirms the molecular formula $C_{15}H_{24}$. In conformity with the findings of Goudie (*loc. cit.*) but contrary to those of Birrell (*loc. cit.*), no crystalline nitrosite, nitrosate, nitrosochloride, or hydrochloride could be prepared. Prolonged hydrogenation (335 hours) of the sesquiterpene in acetic acid using Adams's platinum oxide catalyst gave a product whose analytical figures suggested that uptake of hydrogen corresponding to nearly two double bonds had taken place; perbenzoic acid titration of this hydrosesquiterpene indicated a slight residual unsaturation. A determination of the unsaturation of the sesquiterpene itself with perbenzoic acid gave figures corresponding to an uptake of two atoms of oxygen. On the basis of the degradation of the sesquiterpene to a monocyclic compound of known structure, however, we conclude that the sesquiterpene is monocyclic and must therefore contain three double bonds. One of these might be resistant to hydrogenation and attack by perbenzoic acid, but an alternative explanation is provided below. Two double bonds appear to be conjugated, as reaction occurs with maleic anhydride, although the product decomposes on attempted distillation and has not yet been isolated in a pure state. Sodium and alcohol reduction yields mainly resinous materials. The molecular refraction of (+)-γ-curcumene (68·1) also shows an exaltation over that calculated for a monocyclic sesquiterpene (67·8) which, although small, is considered significant and not due to contamination with other sesquiterpenes. The absorption spectrum in *cyclo*hexane (Fig. 1) shows an absorption maximum at 2670 A. ($\varepsilon_{max.}$ 3500) which, on the basis of the findings of Booker, Evans, and Gillam (*J.*, 1940, 1453) on the absorption spectra of monocyclic dienes of the type of α-phellandrene and α-terpinene, would indicate that the two conjugated double bonds are present in the ring system. Such dienes are characterised by abnormally low $\varepsilon_{max.}$ values as compared with the acyclic and semicyclic dienes.



(I.) (II.) (III.) (IV.)

Birrell (*loc. cit.*) showed that on dehydrogenation his specimen of (+)-γ-curcumene yielded cadalene, and this has been confirmed. Dehydrogenation with sulphur at 270° yielded cadalene, identified as the picrate, which may be compared with the formation of cadalene (II) from zingiberene (I) under similar conditions (Ruzicka, Meyer, and Mingazzini, *Helv. Chim. Acta*, 1922, **5**, 345). Zingiberene, however, is conjugated in the side chain and it might be expected that a *cyclo*hexadiene would tend to form a derivative of benzene. It was found, in fact, that selenium dehydrogenation of (+)-γ-curcumene at 280° gave an isomeric hydrocarbon, $C_{15}H_{24}$. If the structure (III) be accepted for γ-curcumene, then such an isomerisation could arise by an intramolecular disproportionation (cf. Linstead, Michaelis, and Thomas, *J.*, 1940, 1139) and would be expected to yield 6-*p*-tolyl-2-methylheptane (IV). This compound was obtained by Ruzicka and van Veen (*Annalen*, 1929, **468**, 143) in an impure form by dehydrogenation of hexahydrozingiberene with palladised charcoal, and subsequently synthesised. The physical properties of our hydrocarbon, however, differ from those recorded by Ruzicka *et al.* for their specimen of (IV) and the relationship of the two substances is not yet clear. This aspect of the problem is being further investigated. The possibility of our dehydrogenation product being α-curcumene (see below) is excluded since it does not form a nitrosate.

FIG. 1.

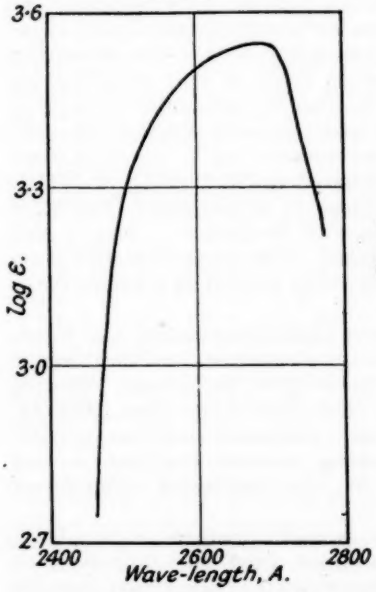
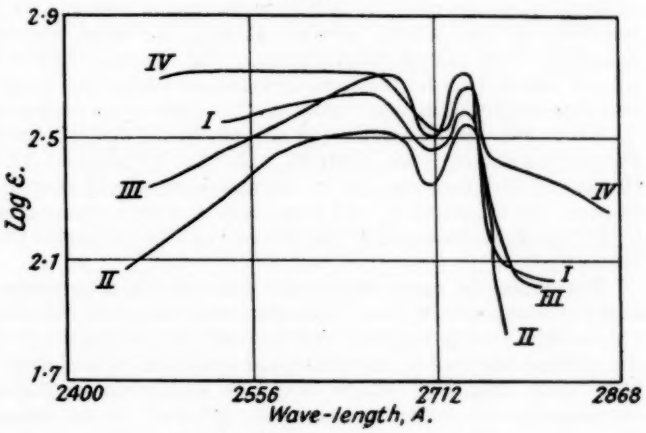


FIG. 2.

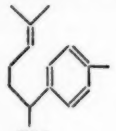


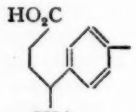
I. C_{13} *acid.*
II. *Ester of* C_{13} *acid.*
III. γ-p-*Tolyl*-n-*valeric acid.*
IV. *Neutral ozonolysis product.*

Oxidative degradation of (+)-γ-curcumene gave valuable information. Birrell (*loc. cit.*) had identified acetone as an ozonolysis product, but no trace of formic acid or formaldehyde was observed. The formation of acetone has been confirmed, and except in one case where a slightly impure specimen of the sesquiterpene was ozonised, no formaldehyde was detected, indicating that the side chain must terminate substantially in the *iso*propylidene arrangement. From larger-scale ozonolysis, in addition to acetone and acetone peroxide, it was possible to isolate a neutral liquid product and a dextrorotatory acid, analysed as the *methyl* ester, $C_{13}H_{18}O_2$, and characterised as the p-*phenylphenacyl* ester, m. p. 74°, and the S-*benzylthiuronium* salt, m. p. 139—139·5°. The acid on further degradation with alkaline permanganate gave terephthalic acid, characterised as the dimethyl ester. Presumably the aromatic ring of terephthalic acid is present in the C_{13} acid and its (C_{13}) ester, and the ultra-violet absorption spectra of both the crude acid and the pure ester (Fig. 2) show the typical resolved absorption for a compound containing a benzene nucleus (Webb, *J. Org. Chem.*, 1939, **4**, 389; Jones, *Chem. Reviews*, 1943, **32**, 1). (−)-γ-*p*-Tolyl-*n*-valeric acid (VI) was isolated by Carter, Copp, Rao, Simonsen, and Subramaniam (*J.*, 1939, 1504) as an ozonolysis product of (−)-α-curcumene (V), its *p*-phenylphenacyl ester melting at 73—74°. The C_{13} acid is therefore formulated as the dextro-form of (VI).

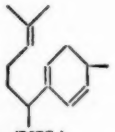
A specimen of racemic γ-*p*-tolyl-*n*-valeric acid (VI) was prepared; the p-*phenylphenacyl*

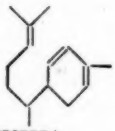
ester melts at 69—69·5° and, mixed with the *p*-phenylphenacyl ester (m. p. 74°) of the ozonolysis acid, at 70—70·5°. Its absorption spectrum (Fig. 2) is closely similar to that of the dextrorotatory ozonolysis acid and its methyl ester.


(V.)



(VI.)


(VII.)


(VIII.)

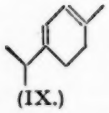
It is difficult to avoid the conclusion that the action of ozone upon the sesquiterpene has resulted in the conversion of a *cyclo*hexadiene structure into the aromatic state in addition to its normal action upon the double bond of the side chain. It is known that such dehydrogenations may be effected in polynuclear systems with, for example, selenium dioxide (Robinson and Slater, *J.*, 1941, 376), and α-terpinene on oxidation with chromyl chloride gives derivatives of benzene (Henderson and Cameron, *J.*, 1909, **95**, 969), but we are not aware of any case where ozone has been found to bring about this change. It may be significant that the percentage of ozone in the stream of gases from the ozoniser was low.

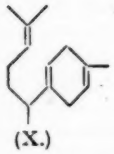
The neutral product from ozonolysis could not be distilled without decomposition. An impure 2 : 4-dinitrophenylhydrazone was prepared, m. p. 85—86°, and oxidation with either neutral permanganate or silver oxide gave (+)-γ-*p*-tolyl-*n*-valeric acid. The absorption spectrum of the neutral product showed the same absorption band as that given by the ozonolysis acid and its methyl ester. The neutral product is probably substantially (+)-γ-*p*-tolyl-*n*-valeraldehyde, the enantiomorph of which (m. p. of dinitrophenylhydrazone, 94—95°) was obtained by Simonsen *et al.* (*loc. cit.*) as one of the products of ozonolysis of (−)-α-curcumene.

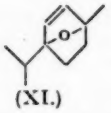
From the above results the sesquiterpene may be formulated as (III), (VII), or (VIII). Baeyer has shown (*Ber.*, 1894, **27**, 815) that α-terpinene (IX) may be distinguished from other closely related terpenes by its characteristic rapid reaction with Beckmann's chromic acid reagent, accompanied by the formation of brown resinous flakes. This reaction is also given by (+)-γ-curcumene and in the absence of other evidence this points to (III) as the most likely structure.

The obviously close relationship between the sesquiterpene under examination and the α- and β-curcumenes (V and X, respectively) suggests the name γ-curcumene. α-Curcumene is not strictly a sesquiterpene, and it would be preferable to rename it *ar.*-curcumene, following the method adopted in the analogous tumerone series (Rupe *et al.*, *Helv. Chim. Acta*, 1934, **17**, 372; 1936, **19**, 569), where both the sesquiterpene (ketone), tumerone, and its aromatic counterpart, *ar.*-tumerone, are also known. It is interesting to note that the α- and β-curcumenes of *C. aromatica* are accompanied by about 1—2% of a conjugated hydrocarbon (Simonsen *et al.*, *loc. cit.*).

In connection with the conversion of (+)-γ-curcumene into aromatic products on ozonolysis, it may be significant that Simonsen *et al.* (*loc. cit.*) isolated from the ozonolysis of (−)-β-curcumene, regenerated from its hydrochloride, small amounts of the degradation products of (−)-α-curcumene. It is stated that the (−)-β-curcumene was not pure, but the characteristic nitrosate of (−)-α-curcumene could not be prepared from it, and hence if α-curcumene were present it must have been in small amount only. An alternative explanation is that the removal of hydrogen chloride from (−)-β-curcumene trihydrochloride forms, in addition to the main product, (−)-β-curcumene (X), smaller amounts of (−)-γ-curcumene which on ozonolysis would give the degradation products of (−)-α-curcumene.


(IX.)


(X.)



(XI.)

The ready passage of the conjugated *cyclo*hexadiene system into the aromatic state may also account for the anomalous hydrogenation results obtained with (+)-γ-curcumene. It is known, for example, that piperitone (Read, Watters, Robertson, and Hughesdon, *J.*, 1929, 2068) and carvone (Linstead *et al.*, *loc. cit.*) undergo partial disproportionation to the corresponding phenols on hydrogenation at room temperature, the uptake of hydrogen, at first rapid, becoming very

slow in the final stages owing to the comparative resistance of the aromatic material to hydrogenation. Finally, it may be noted that Elson, Gibson, and Simonsen (*J.*, 1929, 2732) have shown that the action of perbenzoic acid upon α-terpinene (IX) results in 1 : 4-addition with the formation of 1 : 4-oxido-Δ^2-*p*-menthene (XI), and it might therefore be expected that a structure such as (III) would show similar behaviour and absorb two, rather than three atoms of oxygen when treated with perbenzoic acid.

Experimental.

(+)-*γ-Curcumene*.—The main portion of the sesquiterpene fraction of *L. bidwillii*, distilled through a Lecky and Ewell column of 39 plates, had the following constants: b. p. 94°/3 mm., $d_4^{20°}$ 0·8810, $n_D^{25°}$ 1·4975, $[\alpha]_D$ +31·78° (Found: C, 88·3; H, 11·7. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%). No crystalline derivatives were obtained in attempted preparations of the nitrosochloride, nitrosite, nitrosate, and hydrochloride. The absorption spectrum in spectroscopically pure *cyclo*hexane solution, successively diluted, showed an absorption maximum at 2670 A. and an extinction coefficient of 3500. With maleic anhydride an unstable adduct was obtained which decomposed on attempted distillation. Reduction with sodium in hot alcoholic solution gave mainly a resinous solid.

When a chloroform solution of perbenzoic acid was added to (+)-*γ-curcumene* (0·308 g.), and the mixture kept at 0° until the iodine titre was constant, the oxygen absorption corresponded to 6·24 milliequiv. (Calc. for two double bonds: 6·04).

Hydrogenation of (+)-*γ-Curcumene*.—(*a*) A solution of (+)-γ-curcumene (4 g.) in glacial acetic acid (40 c.c.) was shaken for 335 hours with freshly-prepared Adams's catalyst (0·12 g.) under a pressure of 2 atm. of hydrogen, with periodic reactivation of the catalyst. The redistilled product (3·4 g.) had the following constants: b. p. 106°/2 mm., $n_D^{25°}$ 1·4736, $d_{20°}^{20°}$ 0·8551, $[\alpha]_D$ +11·1° (Found: C, 87·2; H, 13·3. $C_{15}H_{26}$ requires C, 87·4; H, 12·6. $C_{15}H_{28}$ requires C, 86·5; H, 13·5%). Perbenzoic acid titration indicated the presence of slight residual unsaturation (0·060 milliequiv. of oxygen absorbed. Calc. for one double bond, approx. 0·511). Molecular refraction (*M*, 208), 68·5 (Calc. for a dihydromonocyclic sesquiterpene, 68·33; for a tetrahydromonocyclic sesquiterpene, 68·8).

(*b*) A solution of (+)-γ-curcumene (4·6 g.) in absolute alcohol was shaken with hydrogen in the presence of palladised strontium carbonate. The reduction was stopped when the calculated volume of hydrogen for the saturation of one double bond had been absorbed. Distillation of the product gave two fractions, b. p. 90—92°/1·5 mm. (2·54 g. of a colourless mobile liquid) and 134°/1 mm. (0·8 g. of a very viscous yellow oil, $n_D^{25°}$ 1·4915). The lower-boiling fraction had the following constants: $n_D^{25°}$ 1·4856, $d_{20°}^{20°}$ 0·8735, $[\alpha]_D$ +18·6°, $[R_L]_D$ 67·95.

Dehydrogenation of (+)-*γ-Curcumene*.—(*a*) A mixture of (+)-γ-curcumene (7 g.) and finely powdered selenium (7 g.) was heated to 250° and the temperature then gradually raised to 280° and held there for 50 hours. Extraction of the mixture with ether and distillation of the product yielded a blue liquid (4·6 g.), b. p. 130°/6 mm., which was treated by Sherndal's method (*J. Amer. Chem. Soc.*, 1915, **37**, 167) for the isolation of azulene, but only a small quantity of a dark green oil, which did not give a picrate, was obtained. The oil remaining from the azulene extraction was redistilled over sodium. The distillate, b. p. 130°/6 mm., n_D^{25} 1·4932, $d_{20°}^{16°}$ 0·875, was a colourless mobile oil from which no picrate was obtained (Found: C, 88·2; H, 11·7. Calc. for $C_{15}H_{24}$: C, 88·2; H, 11·8%).

(*b*) A mixture of (+)-γ-curcumene (5·0 g.) and flowers of sulphur (2·5 g.) was heated at 270° for 6 hours. The liquid obtained from the ether extraction was distilled, and the distillate (2·4 g.) separated by distillation over sodium into two fractions, b. p. 138—141°/9 mm. and 150—170°/9 mm. On treatment of the higher-boiling fraction with the calculated quantity of picric acid dissolved in the minimum amount of hot alcohol, heating on the water-bath for 15 minutes, and then cooling, an intensely red solution was obtained which deposited long orange needles; m. p., after repeated crystallisations from alcohol, 114°. No mixed m. p. depression was observed with an authentic specimen of cadalene picrate (yield, 0·1 g. from 0·2 g. of distillate). Under similar conditions the lower-boiling fraction gave only picric acid.

Ozonolysis of (+)-*γ-Curcumene*.—(*a*) Pure (+)-γ-curcumene (10 g.) was ozonised in pure carbon tetrachloride until a portion of the solution no longer decolorised a solution of bromine in carbon tetrachloride. The solid ozonide was filtered off, and the filtrate evaporated under reduced pressure. The residue was combined with the solid ozonide, and after standing overnight with water (20 c.c.) was heated under reflux on a water-bath for one hour. The low-boiling material was distilled, yielding a distillate (A), a solid (B) which crystallised in the condenser, and a residue (C). (A) formed a 2 : 4-dinitrophenylhydrazone, m. p. 124—125° alone and mixed with an authentic specimen of acetone 2 : 4-dinitrophenylhydrazone, but no positive tests were obtained for formic acid or formaldehyde. (B), recrystallised from ether, had m. p. 131—133° and sublimed readily, even at room temperature, and no smell of formaldehyde was noticed on heating; combustion was difficult owing to the readiness with which the compound exploded (Found: C, 41·1; H, 6·67. Calc. for CH_2O: C, 40·0; H, 6·6%). (C) was extracted repeatedly with ether, and the combined ether extracts shaken out with 2N-sodium carbonate solution. The residual ethereal layer gave a pale yellow, pleasant-smelling liquid (D, 3·5 g.) which suffered extensive decomposition on attempted distillation. The acid (E, 2 g.) obtained from the sodium carbonate extract was esterified with diazomethane and distilled (with considerable decomposition) to yield a pale yellow liquid (1 g.), b. p. 105—110°/2 mm. In none of a series of small-scale ozonolyses of the pure material was the formation of formaldehyde observed.

(*b*) A larger sample (17·1 g.) of a slightly less pure specimen was ozonised as described above, and in this case by passing the gases from the reaction vessel through water and changing the water several times it was possible to detect the liberation first of acetone (formation of 2 : 4-dinitrophenylhydrazone) and then of formaldehyde (formation of a 2 : 4-dinitrophenylhydrazone, m. p. 165—166°, undepressed by mixing with an authentic specimen). The neutral fraction (D, above) of the decomposed ozonide

amounted to 5·6 g. It furnished a red tarry product with alcoholic 2 : 4-dinitrophenylhydrazine which on repeated extraction with hot alcohol gave a solid. Repeated recrystallisation gave a small amount of material, m. p. 85—86°. Attempts to prepare a crystalline semicarbazone were unsuccessful. The absorption curve of the impure neutral material, dissolved in rectified spirits and successively diluted, had absorption maxima at 2600 A. (approx.) and 2735 A.; $\varepsilon_{max.}$ values are not significant owing to the impure state of the material.

The acid fraction (E, above), amounting to 7·7 g., had $[\alpha]_D$ +19·2°, and on esterification with diazomethane and distillation (twice) the *methyl* ester of (+)-*γ*-*p*-tolyl-*n*-valeric acid was obtained, b. p. 106°/2—3 mm. (Found: C, 75·2; H, 9·75. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·74%). The acid was characterised as the S-*benzylthiuronium* salt, m. p. (from alcohol) 139—139·5° (Found: N, 7·7. $C_{20}H_{26}O_2N_2S$ requires N, 7·8%), and the p-*phenylphenacyl* ester, m. p. 74° (from methanol) (Found: C, 80·4; H, 7·31. $C_{26}H_{26}O_3$ requires C, 80·8; H, 6·7%). The absorption spectrum of the acid was determined in absolute alcohol; absorption maxima occurred at 2735 and at 2665 A. with $\varepsilon_{max.}$ values of 398 and 426, respectively. The absorption spectrum of the purified methyl ester was determined in alcoholic solution; absorption maxima occurred at 2735 and 2670 A. with $\varepsilon_{max.}$ values of 355 and 330, respectively.

Oxidation of the Neutral Fraction (*D*) [(+)-*γ*-p-*Tolyl*-n-*valeraldehyde*?].—A solution of the neutral fraction (D, 4·0 g.) in acetone (120 c.c.) and water (20 c.c.) was heated under reflux, and finely powdered potassium permanganate (21 g.) was gradually added until there was no further decolorisation. The product was filtered, the acetone removed, and the residue extracted with ether. By shaking out the ethereal solution with aqueous sodium carbonate solution (+)-*γ*-*p*-tolyl-*n*-valeric acid (1·5 g.) was obtained and characterised as the *p*-phenylphenacyl ester, m. p. and mixed m. p. 73—74°.

Oxidation of (+)-*γ*-p-*Tolyl*-n-*valeric Acid* (*E*).—The acid fraction of the ozonolysis product (3 g.) in aqueous sodium carbonate was treated under reflux with a 4% aqueous solution of potassium permanganate, the reaction being complete after the addition of 18 g. of permanganate. The product was decolorised with sulphur dioxide, boiled with concentrated sodium hydroxide solution, filtered through sintered glass, and acidified. The white solid (0·5 g.) which separated was centrifuged off and dried. It had no definite m. p. but started to sublime at 280°. The methyl ester melted at 139—140° and showed no depression with authentic methyl terephthalate.

Racemic γ-p-Tolyl-n-valeric Acid.—*γ*-*p*-Tolylpentenoic acid (Rupe and Steinbach, *Ber.*, 1911, **44**, 584; 0·75 g.) in absolute alcohol (35 c.c.) was hydrogenated in the presence of palladised strontium carbonate (0·5 g.), the reaction proceeding rapidly. After removal of the catalyst the solution was made alkaline, the alcohol distilled off, and the product acidified and extracted with ether. The acid was obtained as a clear viscous liquid (0·72 g.) which crystallised after standing for some weeks; m. p. 30—31° (Rupe and Steinbach give m. p. 32°). The p-*phenylphenacyl* ester melted at 69—69·5° (Found: C, 80·7; H, 6·7. $C_{26}H_{26}O_3$ requires C, 80·8; H, 6·7%). A mixture with the *p*-phenylphenacyl ester of (+)-*γ*-*p*-tolyl-*n*-valeric acid melted at 70—70·5°.

The authors are greatly indebted to Mr. C. L. Carter, M.Sc., for performing the micro-analyses, and one of them (R. D. B.) acknowledges the tenure of a John Edmond Research Fellowship.

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181. *Polycyclic Aromatic Hydrocarbons. Part XXXIII. Synthesis of Naphtho(1′ : 2′-1 : 2)fluorene and Naphtho(2′ : 1′-2 : 3)fluorene.*

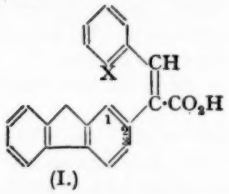
By J. W. COOK and (MISS) E. F. M. STEPHENSON.

1 : 2 : 7 : 8-Dibenzanthracene (VI; X = H) has been synthesised by an improved method and transformed, through its 3 : 4-*quinone* (VIII), into *naphtho*(2′ : 1′-2 : 3)*fluorene* (X). The isomeric *naphtho*(1′ : 2′-1 : 2)*fluorene* (II; X = H) has been synthesised from fluorene-2-acetic acid by the Pschorr method and found to be carcinogenic and also to inhibit tumour-growth. Indane-1 : 2-dicarboxylic acid has been prepared in *cis*- (XVII) and *trans*-forms (XVIII), characterised as their *methyl* esters.

As part of a study of the inhibitory effects on tumour growth of polycyclic aromatic compounds related to the carcinogenic hydrocarbons, it was desired to synthesise *naphtho*(2′ : 1′-2 : 3)-*fluorene* (X). Some preliminary experiments towards this objective were recorded by Cook and Preston (*J.*, 1944, 553). After further exploratory work summarised below, methods were devised by which we have been able to obtain the required hydrocarbon (X), and also the isomeric *naphtho*(1′ : 2′-1 : 2)*fluorene* (II; X = H). In tests carried out by Professor A. Haddow, which will be reported elsewhere, (II; X = H) has given clear evidence of inhibition of growth of transplanted tumours in rats and has also given malignant tumours of the skin in mice. The isomeric hydrocarbon is still under test.

Naphtho(1′ : 2′-1 : 2)fluorene (II; X = H) was obtained by a series of reactions by which it had been hoped to prepare the isomer (X). For this purpose, the Pschorr phenanthrene synthesis was adopted. Fluorene-2-acetic acid was condensed with *o*-nitrobenzaldehyde to give o-*nitro*-*α*-2-*fluorenylcinnamic acid* (I; X = NO_2), which was reduced to the corresponding *amino-acid* (I; X = NH_2). Diazotisation of this was troublesome, but was accomplished with

amyl nitrite and ethanolic hydrochloric acid. The resulting diazonium salt underwent cyclisation to *naphtho*(1′ : 2′-1 : 2)*fluorene-3′-carboxylic acid* (II; X = CO_2H) when its suspension in ethanol was treated with copper powder. The acid was decarboxylated by heating it with copper powder, the hydrocarbon (II; X = H) being sublimed under reduced pressure. Oxidation of (II; X = H) with sodium dichromate in boiling acetic acid gave a mixture, which was separated by chromatography into *naphtho*(1′ : 2′-1 : 2)*fluorenone* (III) and the *quinone* (IV). In an attempt to adapt the method developed by Hewett (*J.*, 1938, 1286; 1940, 293) to the synthesis of benzologues of phenanthrene, fluorene-2-acetic acid was condensed with *o*-chlorobenzaldehyde to give o-*chloro*-α-2-*fluorenylcinnamic acid* (I; X = Cl). However, this acid could not be cyclised by fusion with alkali.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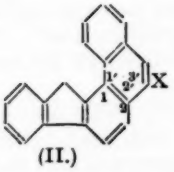
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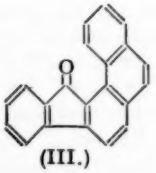
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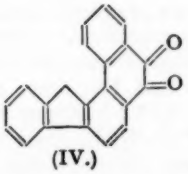
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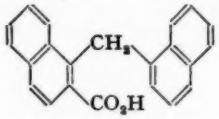
The Pschorr ring-closure of the diazonium salt from the amino-acid (I; X = NH_2) could take place at positions 1 or 3 of the fluorene system. Only one of these positions was attacked, for the product was homogeneous. The actual direction of cyclisation, *i.e.*, at position 1, was unexpected, for both ω-2-fluorenyl-*o*-toluic acid (Barnett, Goodway, and Watson, *Ber.*, 1933, **66**, 1880) and γ-2-fluorenylbutyric acid (Koelsch, *J. Amer. Chem. Soc.*, 1933, **55**, 3885) undergo cyclisation at position 3 of the fluorene system. The structures assigned to the products which we obtained are based on the finding that the hydrocarbon (II; X = H) and its oxidation product (III) differ from naphtho(2′ : 1′-2 : 3)fluorene (X) and the corresponding fluorenone (IX), which would have been obtained if cyclisation had occurred at position 3 of the fluorene nucleus in (I).

The starting point in the synthesis of naphtho(2′ : 1′-2 : 3)fluorene (X) was 1 : 2 : 7 : 8-dibenzanthracene (VI; X = H), two syntheses of which have been recorded (Cook, *J.*, 1932, 1472; cf. Waldmann, *J. pr. Chem.*, 1932, **135**, 1). In order to obtain this hydrocarbon in quantity adequate for our present purpose, it was found necessary to improve the method selected for its preparation. To this end, 2-carboxy-1 : 1′-dinaphthyl ketone, an intermediate used by Cook (*loc. cit.*) in one route to (VI) was reduced by Huang–Minlon's modification (*J. Amer.*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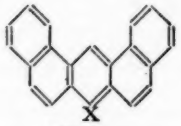
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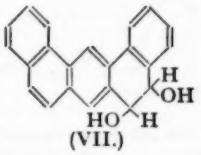
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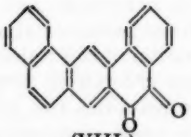
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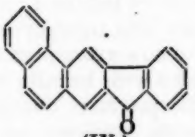
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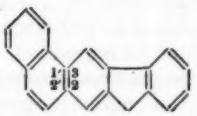
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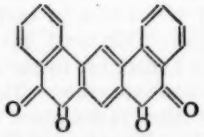
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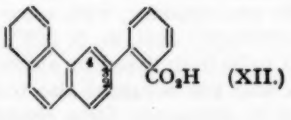
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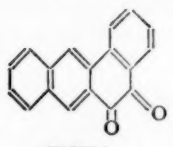
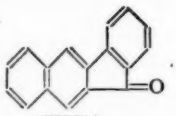
Chem. Soc., 1946, **68**, 2487) of the Wolff–Kishner method. This led to 1 : 1′-*dinaphthylmethane*-2-*carboxylic acid* (V), now obtained crystalline and analytically pure, which with a boiling mixture of acetic acid and acetic anhydride, containing a little zinc chloride (compare Fieser and Hershberg, *ibid.*, 1937, **59**, 1028), was converted in good yield into 10-acetoxy-1 : 2 : 7 : 8-dibenzanthracene (VI; X = OAc). For hydrolysis to the anthranol (VI; X = OH) the procedure of Fieser and Hershberg (*loc. cit.*) was used, whereby the acetate was treated with

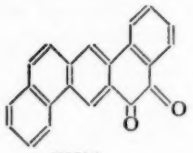
n-butylmagnesium bromide. The final reduction, of the anthranol to 1 : 2 : 7 : 8-dibenzanthracene, (VI; X = H) was effected with zinc dust and aqueous alkali in presence of toluene (compare Martin, *ibid.*, 1936, **58**, 1438.)

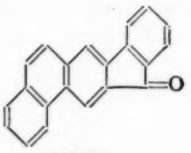
Osmium tetroxide in benzene–pyridine reacted by addition with 1 : 2 : 7 : 8-dibenzanthracene (compare Criegee, Marchand, and Wannowius; *Annalen*, 1942, **550**, 99) to give a coloured complex which was then hydrolysed to a diol; this, from the work of Cook and Schoental (*J.*, 1948, 170), should have the structure (VII). The diol was difficult to purify, but was characterised by the preparation of its *diacetate* and by conversion into 3-(or 4-)*methoxy*-1 : 2 : 7 : 8-*dibenzanthracene*. Oxidation of the diol (VII) with sodium dichromate in acetic acid gave 1 : 2 : 7 : 8-*dibenz*-3 : 4-*anthraquinone* (VIII) as the main product, together with 1 : 2 : 7 : 8-*dibenz*-3 : 4 : 5 : 6-*anthradiquinone* (XI). (VIII) reacted with *o*-phenylenediamine to give a *phenazine* derivative, and the presence of two *ortho*-quinonoid groups in (XI) was shown by its reaction with two molecules of *o*-phenylenediamine. The monoquinone was obtained free from diquinone when the diol (VII) was oxidised by means of ethyl azodicarboxylate (Diels and Fritzsche, *Ber.*, 1911, **44**, 3022).

1 : 2 : 7 : 8-Dibenz-3 : 4-anthraquinone (VIII) was smoothly converted into *naphtho*-(2′ : 1′-2 : 3)*fluorenone* (IX) by being heated with lead monoxide, and the formation of a coloured ketone in this way confirms the structures assigned to the diol (VII) and its oxidation products. The ketone was finally reduced to naphtho(2′ : 1′-2 : 3)fluorene (X) by heating it in a sealed tube with hydrazine hydrate. The degradation of (VIII) to (IX) probably involves a benzilic acid transformation, in which case the structure of the product is not in doubt. If, however, the acid (XII) were formed as an intermediate, then its cyclisation to a fluorenone could take place not only at position 2 of the phenanthrene system, but also at position 4, and the latter position might be preferentially attacked. This would lead to a ketone of the structure (III). Nevertheless, it seems certain that the transformation of (VIII) into (IX) has been correctly interpreted, for parallel degradations have been carried out in which all of the possible products are known compounds of established structure. Thus, 1 : 2-benz-3 : 4-anthraquinone (XIII), on being heated with lead monoxide, gave exclusively 2 : 3-benzfluorenone (XIV) and not the isomeric 1 : 2-benzfluorenone, and in experiments which will be reported later we have found that 1 : 2 : 5 : 6-dibenz-3 : 4-anthraquinone (XV) is converted into naphtho(1′ : 2′-2 : 3)fluorenone (XVI) (Cook *et al.*, *J.*, 1935, 1319) and not the alternative naphtho(2′ : 1′-1 : 2)fluorenone (Cook *et al.*, *J.*, 1934, 1727).


(XIII.)


(XIV.)

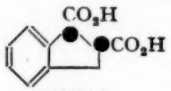

(XV.)

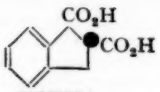

(XVI.)

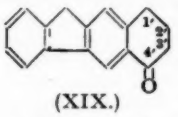
One of the methods considered by Cook and Preston (*loc. cit.*) for the synthesis of naphtho-(2′ : 1′-2 : 3)fluorene (X) involved the use of indane-1 : 2-dicarboxylic anhydride, and, although this anhydride was prepared, the work was interrupted before the subsequent stages of the synthesis could be examined. We have now attempted the condensation of this anhydride with β-naphthylmagnesium bromide, and also with tetralin by aluminium chloride in nitrobenzene. In view of the small amounts of acidic products obtained in these reactions the method was abandoned. In the course of this work, however, we have made some observations which correct and extend those of Cook and Preston relating to indane-1 : 2-dicarboxylic anhydride. This anhydride was obtained, with some difficulty, by the action of boiling acetyl chloride on the known dicarboxylic acid, m. p. 228°, and, as the anhydride must have the *cis*-configuration and was found to be hydrolysed by alcoholic potassium hydroxide to the acid from which it was prepared, this acid was assumed also to have the *cis*-configuration. This conclusion has now been shown to be erroneous, for a change of configuration takes place under the influence of alkali, and the acid, m. p. 228°, is the *trans*-acid (XVIII). The cis-*acid* (XVII), m. p. 197—198°, was obtained by hydrolysing the anhydride with water. This *cis*-acid was reconverted into the anhydride in good yield by boiling acetyl chloride, or even by distilling its solution in tetrachloroethane. The *cis*-acid was also formed by catalytic hydrogenation of indene-2 : 3-dicarboxylic acid over palladium. These stereoisomeric dicarboxylic acids were characterised by conversion into their *methyl* esters.

In another approach to the synthesis of (X) the action of 1-diethylaminobutan-3-one

methiodide on the keto-tetrahydro-2 : 3-benzfluorene (XIX) was examined (compare du Feu, McQuillin, and Robinson, *J.*, 1937, 53; Cornforth and Robinson, *J.*, 1946, 676; Wilds and


(XVII.)


(XVIII.)


(XIX.)

Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469). This led to no useful result. The ketone (XIX) underwent the Reformatsky reaction with ethyl bromoacetate to give the expected unsaturated *acid*, but no crystalline product could be isolated when a similar condensation was carried out with methyl γ-bromocrotonate.

Experimental.

(All m. p.s are uncorrected. Light petroleum refers to the material, b. p. 40–60°, and ligroin to that boiling at 80—100°.)

Fluorene-2-acetic Acid.—(*a*) Dry hydrogen chloride was passed into a suspension of paraformaldehyde (6 g.; 0·2 mol.) in glacial acetic acid (200 c.c.) until a clear solution was formed. Fluorene (13·3 g.; 0·08 mol.) and powdered anhydrous zinc chloride (0·5 g.) were then added and the passage of hydrogen chloride was continued for ½ hour. The flask was stoppered and kept at room temperature for 5 days. After dilution with ice–water the precipitate was collected and washed with water, then with dilute sodium carbonate solution, and finally with water. The product was largely a mixture of 2-chloromethylfluorene, which could not be isolated in a pure state, with unchanged fluorene. If the reaction was allowed to proceed until all the fluorene was used, the chloromethyl compound was mostly polymerised. The mixture was drained from moisture as far as possible and treated immediately with excess of concentrated aqueous potassium cyanide and sufficient acetone to effect solution. This solution was boiled for 3 hours, the acetone was removed, and the residual oil was diluted with water, whereupon it solidified. In order to hydrolyse the cyanide this solid was refluxed with a mixture of acetic acid and concentrated hydrochloric acid (3 : 1). After the mixture had been diluted with water, the crude product was collected and digested with dilute sodium carbonate solution and the filtered solution was clarified with charcoal and acidified. The precipitated fluorene-2-acetic acid (1·9 g.) had m. p. 178—180°. Sublimation, at 0·4 mm., of the neutral material insoluble in sodium carbonate gave 7·8 g. of unchanged fluorene. The residue from this sublimation was heated at 225—240°/0·015 mm., and gave a crystalline sublimate of 2 : 2′-difluorenylmethane, m. p. 201—202° (after recrystallisation from acetic acid and then light petroleum) (Found : C, 94·1; H, 5·8. Calc. for $C_{27}H_{20}$: C, 94·2; H, 5·8%). Dziewónski and Panek (*Bull. Acad. Polonaise, A*, 1927, 745), who obtained this hydrocarbon by the action of phosphoric oxide on a solution of fluorene and methylal in chloroform, give m. p. 201—202°.

(*b*) Much better results were obtained by the Willgerodt reaction with 2-acetylfluorene (Bachmann and Sheehan, *J. Amer. Chem. Soc.*, 1940, **62**, 2687), taking advantage of the finding of De Tar and Carmack (*ibid.*, 1946, **68**, 2028) that a reproducible ammonium sulphide reagent can be prepared by suspending in concentrated ammonia solution one-tenth of its weight of sulphur and passing in hydrogen sulphide until this just dissolves. A mixture of 2-acetylfluorene (3 g.), ammonium sulphide reagent (12·5 c.c.), and dioxan (peroxide-free; 15 c.c.) was heated for 8 hours at 160—170° in a small stainless-steel autoclave. The contents of the autoclave were washed out with ethanol and the solution evaporated on the steam-bath. A solution of the residual crude amide in acetic acid (40 c.c.) and concentrated hydrochloric acid (12 c.c.) was boiled for 7 hours and then poured into water. The precipitate was dissolved in hot dilute sodium carbonate solution, filter aid was added, and the filtered solution was acidified. The precipitated fluorene-2-acetic acid was recrystallised from 50% ethanol (charcoal), m. p. 175—177° (1·8 to 2·0 g.). When the acid was further purified by sublimation at 0·003 mm. and then crystallised from benzene, it had m. p. 183°. Bachmann and Sheehan (*loc. cit.*) give m. p. 186—187°, whereas von Braun and Engel (*Ber.*, 1924, **57**, 194) give m. p. 178° for a recrystallised acid prepared by hydrolysis of the cyanide.

o-*Nitro-α-2-fluorenylcinnamic Acid* (I; X = NO_2).—In the Perkin condensation of fluorene-2-acetic acid with *o*-nitrobenzaldehyde the triethylamine salt was found to give better yields than did the sodium salt (compare Kalnin, *Helv. Chim. Acta*, 1928, **11**, 977; Bakunin and Peccerillo, *Gazzetta*, 1935, **65**, 1145). A mixture of fluorene-2-acetic acid (5·6 g.; dried at 110°), *o*-nitrobenzaldehyde (4 g.), triethylamine (2·52 g. = 3·45 c.c.; dried over potassium hydroxide), and "Analar" acetic anhydride (30 c.c.) was heated for 11 hours in an oil-bath at 85—95°. The pale-brown solution was poured, while still warm, into vigorously stirred cold water (250 c.c.), and the whole kept for 12 hours and then heated on the water-bath until the viscous precipitate was completely solid (1—2 hours). This was collected, washed, and, without drying, dissolved in hot benzene (*ca.* 230 c.c.). The solution was cooled, filtered to remove a little *o*-nitrocinnamic acid, and then exhaustively extracted with dilute sodium carbonate solution. The alkaline extract was warmed with charcoal and filtered, and the crude acid was precipitated with hydrochloric acid (yield, 8·75 g.). After recrystallisation from 50% acetic acid, then 50% ethanol, and finally benzene–ligroin, o-*nitro-α-2-fluorenylcinnamic acid* formed bright yellow needles, m. p. 215—216° (decomp.) (Found : C, 74·2; H, 4·3; N, 3·9. $C_{22}H_{15}O_4N$ requires C, 73·9; H, 4·2; N, 3·9%).

o-*Chloro-α-2-fluorenylcinnamic Acid* (I; X = Cl).—A mixture of sodium fluorene-2-acetate (1·35 g.), *o*-chlorobenzaldehyde (0·77 g.), and acetic anhydride (7·5 c.c.) was heated for 8 hours in an oil-bath at 130—140°. After decomposition with water as in the previous example, the product was washed with hot water. The washings, on cooling, deposited crystals of *o*-chlorocinnamic acid. The insoluble residue was purified by dissolution in sodium carbonate solution and reprecipitation, followed by

recrystallisation from aqueous acetone and then benzene. The *acid* (I; X = Cl) formed colourless needles, m. p. 229—231° (Found : C, 76·1; H, 4·4; Cl, 10·3. $C_{22}H_{15}O_2Cl$ requires C, 76·2; H, 4·4; Cl, 10·2%). From the material insoluble in sodium carbonate there was isolated a neutral compound which formed pale yellow crystals (from ligroin), m. p. 138—139° (Found : C, 83·4; H, 4·8; Cl, 11·2. $C_{21}H_{15}Cl$ requires C, 83·3; H, 5·0; Cl, 11·7%); this was evidently trans-2-*o*-*chlorostyrylfluorene*.

o-*Amino*-α-2-*fluorenylcinnamic Acid* (I; X = NH_2).—A solution of the finely powdered crude nitro-acid (I; X = NO_2) (2·7 g.) in water (100 c.c.) and concentrated ammonia (140 c.c.) was added to a solution of ferrous sulphate (22 g.) in warm water (50 c.c.). The suspension so formed was heated on the water-bath for 2 hours. After dilution with hot water, the whole was boiled and filtered. The precipitate was extracted with hot 1% ammonia solution until the washings were free from amino-acid. The combined filtrate and washings were acidified with acetic acid, and the precipitated *amino-acid* was collected (1·9 g.; m. p. 217·5—219·5°), purified by redissolution in sodium carbonate solution, heating with charcoal on the water-bath, reprecipitation with acetic acid and then recrystallisation from ethanol and finally benzene. It formed yellow needles, m. p. 217·5—219·5° (Found : C, 80·9; H, 5·05; N, 4·1. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·25; N, 4·3%). This acid formed sparingly soluble sodium and ammonium salts.

Naphtho(1′ : 2′-1 : 2)*fluorene*-3′-*carboxylic Acid* (II; X = CO_2H).—Diazotisation of the foregoing amino-acid in aqueous solution was always incomplete, and, as both the diazonium salt and the salts of the amino-acid were sparingly soluble in water, it was not feasible to separate them. For complete diazotisation with amyl nitrite it was found advisable to use hydrochloric rather than sulphuric acid and to work at room temperature. A solution of the amino-acid (I; X = NH_2) (1·58 g.) in warm ethanol (250 c.c.) was cooled to 10—15°. Concentrated hydrochloric acid (32 c.c.) was rapidly added, and then, after shaking, redistilled amyl nitrite (3·5 c.c.) was added immediately in one portion. If the temperature rose above 20°, it was brought to this level by cooling and kept there for 1½ hours. Separation of the yellow diazonium chloride began after a few minutes. For decomposition of the diazonium salt, freshly prepared copper powder (Gattermann, *Ber.*, 1890, **23**, 1219) was added and the mixture was shaken at room temperature until a colour was no longer developed with alkaline β-naphthol. The reaction mixture was diluted with cold water to 1200 c.c., and the precipitate was collected and extracted with dilute sodium carbonate solution, and the acid reprecipitated from the filtered solution. After recrystallisation from acetic acid it had m. p. 250—251° (0·9 g.). For analysis, it was recrystallised twice from acetic acid and then from benzene containing 10% of ethanol (Found : C, 85·0; H, 4·4. $C_{22}H_{14}O_2$ requires C, 85·2; H, 4·55%). *Naphtho*(1′ : 2′-1 : 2)*fluorene*-3′-*carboxylic acid* formed small cream-coloured needles, m. p. 251—252·5° (decomp.). It was sparingly soluble in benzene and moderately soluble in acetic acid. In the purification of this acid a less soluble acid, m. p. 269—271° was isolated in amount insufficient for investigation (Found : C, 71·4; H, 4·8%).

Naphtho(1′ : 2′-1 : 2)*fluorene* (II; X = H).—Decarboxylation of the acid (II; X = CO_2H) proved troublesome. A pure compound could not be isolated after heating it with copper powder in quinoline; heating it with copper powder without a solvent gave the hydrocarbon, but it was found best to work with batches of acid not exceeding 0·2 g. An intimate mixture of the acid with 2 parts of dry copper powder was heated at 260—280° for a few minutes in a metal-bath. The mass was then sublimed at 300—320°/0·2—0·4 mm., and the sublimate (yield, *ca.* 20%) was digested with hot 1% sodium hydroxide solution to remove unchanged acid. The residue was dissolved in light petroleum and the solution passed through a column of alumina. Red by-products were strongly adsorbed. The hydrocarbon, which slowly passed down the column, was eluted with light petroleum. Evaporation of the eluate gave *naphtho*(1′ : 2′-1 : 2)*fluorene* (II; X = H), which crystallised from light petroleum as colourless plates, m. p. 158·5—159·5° (Found : C, 94·7; H, 5·2. $C_{21}H_{14}$ requires C, 94·7; H, 5·3%). Crystallisation from alcohol gave needles of somewhat lower m. p. Neither a picrate nor a *s*-trinitrobenzene complex could be obtained.

Oxidation of Naphtho(1′ : 2′-1 : 2)*fluorene*.—A solution of the hydrocarbon (1 part) and sodium dichromate (2 parts) in acetic acid was boiled for 15 minutes and poured into water. The yellow precipitate was dissolved in benzene and the solution was washed with aqueous sodium carbonate, dried (Na_2SO_4), and passed through a column of alumina. The less strongly adsorbed material from a benzene eluate was *naphtho*(1′ : 2′-1 : 2)*fluorenone* (III) which formed orange needles (from ethanol), m. p. 152—153° (Found : C, 90·0; H, 4·4. $C_{21}H_{12}O$ requires C, 90·0; H, 4·3%). A more strongly adsorbed red band was eluted with chloroform; evaporation of this solution gave *indeno*(3′ : 2′-3 : 4)-*phenanthra*-9 : 10-*quinone* (IV), which formed yellow plates (from benzene), m. p. 243—244° (Found : C, 84·4; H, 4·0. $C_{21}H_{12}O_2$ requires C, 85·1; H, 4·1%). Analysis suggested slight contamination with a compound of higher oxygen content, but there was insufficient material for further purification.

1 : 1′-*Dinaphthylmethane*-2-*carboxylic Acid* (V).—A mixture of 2-carboxy-1 : 1′-dinaphthyl ketone (Cook, *J.*, 1932, 1476) (3·26 g.), 90% hydrazine hydrate solution (2·2 c.c.), potassium hydroxide (1·9 g.), and diethylene glycol (bis-2-hydroxyethyl ether) (25 c.c.) was boiled under reflux for 1½ hours. The condenser was then removed and the temperature of the mixture (thermometer in liquid) was allowed to rise to 190—195°. The condenser was then replaced and boiling continued for 6 hours. The solution was poured into water (500 c.c.), whereupon the very sparingly soluble sodium salt (0·6 g.) of the *azine* of the keto-acid was precipitated; this was collected and converted into the free acid which crystallised from acetic acid as cream coloured plates, m. p. 301—303° (Found : C, 81·6; H, 4·5; N, 4·4. $C_{44}H_{28}O_4N_2$ requires C, 81·5; H, 4·3; N, 4·3%). The alkaline filtrate from which the sodium salt had been separated was acidified and extracted with benzene. The benzene extract was freed from resinous impurities by passage through a column of silica, and the solvent was removed. The residue was washed with light petroleum; the acid (1·83 g.) was then almost pure. After several recrystallisations from benzene, 1 : 1′-*dinaphthylmethane*-2-*carboxylic acid* (V) formed colourless crystals, m. p. 207—208° (Found : C, 84·9; H, 5·3. $C_{22}H_{16}O_2$ requires C, 84·6; H, 5·2%). The substance partly fused at 150—170°, but resolidified at a higher temperature.

10-*Acetoxy*-1 : 2 : 7 : 8-*dibenzanthracene*.—For cyclisation of the acid (V) with zinc chloride in acetic anhydride and acetic acid the procedure of Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1937, **59**, 1032;

1938, **60**, 1895) was used. The acetate (VI; X = OAc), obtained in 85% yield, crystallised from benzene containing 15% of ethanol in colourless needles, m. p. 255—256°, in agreement with Cook (*loc. cit.*).

1 : 2 : 7 : 8-*Dibenzanthracene* (VI; X = H).—The powdered acetate (VI; X = OAc) (3·6 g.), suspended in pure dry benzene (60 c.c.), was added to a Grignard solution from magnesium turnings (2·06 g.), *n*-butyl bromide (10·25 c.c.), and absolute ether (50 c.c.). The mixture was boiled for an hour, during which the ether was allowed to distil. Toluene (170 c.c.) was added while the mixture was still warm, and the magnesium complexes were decomposed by addition of dilute hydrochloric acid. The benzene–toluene layer was washed twice with warm water and then immediately treated with zinc dust (8 g.) and 2N-sodium hydroxide (200 c.c.). The whole was boiled under reflux for 8 hours. The mixture was acidified with hydrochloric acid, the benzene–toluene layer was separated, and the aqueous solution and excess of zinc were extracted with benzene. The combined solutions were washed with water and the solvents removed under diminished pressure. The residue was recrystallised from acetic acid, and gave 1 : 2 : 7 : 8-dibenzanthracene (2·17 g.), m. p. 190—191°. After purification by passage through a column of alumina and crystallisation from methanol–benzene; it melted at 197—198° (lit., 196°).

3 : 4-*Dihydroxy*-3 : 4-*dihydro*-1 : 2 : 7 : 8-*dibenzanthracene* (VII).—A solution of 1 : 2 : 7 : 8-dibenzanthracene (1·64 g.) and osmium tetroxide (1·53 g.) in pure dry benzene (62 c.c.) and pyridine (1·44 c.c.) was kept at room temperature until separation of the coloured osmium complex was complete (12 days). The precipitate was collected, washed with benzene, and shaken with methylene chloride (60 c.c.) and 1% potassium hydroxide solution (150 c.c.) containing 10% of mannitol. When hydrolysis of the complex was complete, the diol which had separated (1·41 g.) was filtered from the emulsified mixture, washed with water, and dried. A further quantity (0·1 g.) was recovered from the filtrate. The diol (VII), a colourless solid, m. p. 226—228° (decomp.), crystallised with difficulty and was acetylated with pyridine–acetic anhydride (2 days at room temperature and then 20 minutes at 100°). After chromatographic purification on silica of a benzene solution, 3 : 4-*diacetoxy*-3 : 4-*dihydro*-1 : 2 : 7 : 8-*dibenzanthracene* was obtained as fine colourless needles [from benzene–ethanol; (1 : 1)], m. p. 225—226·5° (Found: C, 78·7; H, 5·05. $C_{26}H_{20}O_4$ requires C, 78·8; H, 5·1%).

The diol was dehydrated by brief boiling of its solution in acetic acid containing a few drops of concentrated hydrochloric acid. The crude phenolic product was methylated with methyl sulphate and sodium hydroxide solution to give 3-(or 4-)*methoxy*-1 : 2 : 7 : 8-*dibenzanthracene* which, after passage through a column of alumina of its solution in light petroleum, formed colourless crystals (from ligroin), m. p. 182·5—183·5° (Found: C, 89·4; H, 5·4. $C_{23}H_{16}O$ requires C, 89·2; H, 5·4%).

1 : 2 : 7 : 8-*Dibenz*-3 : 4-*anthraquinone* (VIII).—(*a*) A mixture of the diol (VII) (0·52 g.) and sodium dichromate (0·5 g.) in water (2 c.c.) and acetic acid (75 c.c.) was boiled for 10 minutes. As the diol dissolved, the red quinone was precipitated. The suspension was diluted with warm water and the precipitate collected and washed with water. By crystallisation from tetrachloroethane this (0·44 g.) was separated into a small amount of the diquinone (see below) and a larger amount of the more soluble monoquinone, m. p. 310°. In order to obtain the latter in a state of analytical purity the crude product was cautiously sublimed at 0·3 mm. Pure 1 : 2 : 7 : 8-*dibenz*-3 : 4-*anthraquinone* (VIII) sublimed first as bright red needles, m. p. 310° (decomp.) (Found: C, 85·8; H, 3·9. $C_{22}H_{12}O_2$ requires C, 85·7; H, 3·9%). By heating with *o*-phenylenediamine in acetic acid this yielded the corresponding *phenazine* derivative as small yellow needles (from tetrachloroethane), m. p. 327—329° (decomp.) (Found: C, 83·8; H, 3·9; N, 7·1. $C_{28}H_{16}N_2$ requires C, 88·4; H, 4·2; N, 7·4%). The analytical discrepancy was accounted for by retention of tetrachloroethane (Found: Cl, 5·6%), even after drying at 140°/10 mm. There was insufficient material for further purification.

The crude diquinone which had been separated during the purification of the oxidised diol was re-treated with sodium dichromate in boiling acetic acid to complete oxidation of the adherent monoquinone. The resulting material was extracted with hot tetrachloroethane, and the insoluble residue was crystallised from diethylene glycol. 1 : 2 : 7 : 8-*Dibenz*-3 : 4 : 5 : 6-*anthradiquinone* (XI) formed small orange needles, m. p. above 340° (decomp.) (Found: C, 78·1; H, 3·2. $C_{22}H_{10}O_4$ requires C, 78·1; H, 3·0%). The corresponding *bis-phenazine* derivative, prepared by treatment with *o*-phenylenediamine in boiling acetic acid, crystallised from *o*-dichlorobenzene in very small yellow crystals, m. p. above 360° (Found: C, 84·7; H, 3·7. $C_{34}H_{18}N_4$ requires C, 84·6; H, 3·8%).

(*b*) A mixture of the diol (VII) (0·16 g.) and ethyl azodicarboxylate (3 g.) was heated in an oil-bath for 11 hours, first at 100—110° and then at 105—115°. The cooled mixure was diluted with ethanol and the suspended product (75 mg.) was collected and washed with ethanol. The 1 : 2 : 7 : 8-dibenz-3 : 4-anthraquinone so obtained had m. p. 300° (decomp.), raised to 310° by recrystallisation from tetrachloroethane.

Naphtho(2′ : 1′-2 : 3)*fluorenone* (IX).—An intimate mixture of the purified quinone (VIII) (0·28 g.) and lead monoxide (2 g.) was divided into 3 portions. Each portion was separately introduced into an apparatus fitted for vacuum sublimation and heated in a metal-bath at 260—270° under atmospheric pressure. After 2 minutes the brisk reaction had subsided, and the pressure was reduced to 0·3 mm. The resulting orange sublimate (110 mg. in all) had m. p. 250·5—251·5°. Recrystallisation from benzene–ethanol (1 : 2) gave small orange needles, m. p. 252—253°, of *naphtho*(2′ : 1′-2 : 3)*fluorenone* (Found: C, 90·0; H, 4·2. $C_{21}H_{12}O$ requires C, 90·0; H, 4·3%).

Naphtho(2′ : 1′-2 : 3)*fluorene* (X).—The ketone (IX) (75 mg.) and 50% hydrazine hydrate solution (0·2 c.c.) were heated in a sealed tube at 200—210° for 7½ hours. The product was purified by passing its solution in light petroleum through a column of alumina and the material recovered by evaporation was recrystallised from ethanol. *Naphtho*(2′ : 1′-2 : 3)*fluorene* formed colourless, almost cubic crystals, m. p. 171·5—173° (Found: C, 94·8; H, 5·35. $C_{21}H_{14}$ requires C, 94·7; H, 5·3%). Another preparation crystallised in plates, m. p. 178·5—179·5°.

Degradation of 1 : 2-*Benz*-3 : 4-*anthraquinone to* 2 : 3-*Benzfluorenone*.—1 : 2-Benz-3 : 4-anthraquinone (XIII), prepared as described by Cook and Schoental (*loc. cit.*), was treated with lead monoxide under the conditions used for the quinone (VIII). The resulting yellow ketone (XIV) had m. p. 150·5—152·5° after recrystallisation from ethanol, and gave an oxime, m. p. 230—231°. 2 : 3-Benzfluorenone has

m. p. 152° and its oxime has m. p. 231°, whereas the alternative 1 : 2-benzfluorenone has m. p. 132·5° and its oxime has m. p. 202° (decomp.).

cis-*Indane*-1 : 2-*dicarboxylic Acid* (XVII).—(*a*) The *cis*-anhydride (Cook and Preston, *loc. cit.*) (0·5 g.) was boiled with water. The molten anhydride dissolved in the course of a few minutes. The cooled solution was kept for a few days during which cis-*indane*-1 : 2-*dicarboxylic acid* crystallised as colourless leaflets, m. p. 197—198° with evolution of gas (Found : C, 64·15; H, 4·8. $C_{11}H_{10}O_4$ requires C, 64·0; H, 4·9%). The *methyl* ester, obtained by treatment with ethereal diazomethane, was distilled at 0·1 mm. from a bath at 100°. The viscous distillate slowly crystallised and had m. p. 71—72°, depressed to 55—60° by admixture with the isomer described below (Found : C, 66·35; H, 6·0. $C_{12}H_{14}O_4$ requires C, 66·6; H, 6·0%). Recrystallisation from hexane gave thick colourless rhombs, m. p. 72—73°. The monoethyl ester described by Cook and Preston (*loc. cit.*) is clearly also a derivative of the *cis*-acid.

(*b*) Indene-2 : 3-dicarboxylic acid (Bougault, *Compt. rend.*, 1914, **159**, 745) (5·1 g.) was hydrogenated in ethanolic suspension (400 c.c.) with palladised charcoal or palladium-black until absorption of hydrogen ceased. The filtered solution was evaporated and the viscous residue rubbed with a little ethyl acetate. The residual solid (2·5 g.) was recrystallised from water and had m. p. 190—192° (decomp.). This was identical with the *cis*-acid, obtained as described under (*a*). A further 1·2 g. of less pure material was obtained by acid hydrolysis of the oil obtained by evaporation of the ethyl acetate washings.

(*c*) Ethyl indene-2 : 3-dicarboxylate (2·6 g.) was hydrogenated as described by Cook and Preston (*loc. cit.*). The liquid product was dissolved in a mixture of acetic acid (3 parts) and concentrated hydrochloric acid (1 part), and the solution was boiled for 4 hours, after which no turbidity resulted from dilution with water. Crystalline material had separated, and the amount was augmented by diluting with water. It (1·9 g.) had m. p. 187—189° (decomp.) and was essentially *cis*-indane-1 : 2-dicarboxylic acid.

trans-*Indane*-1 : 2-*dicarboxylic acid* (XVIII).—The known dicarboxylic acid, m. p. 228°, was formed when the *cis*-anhydride (0·5 g.) was heated on the water-bath for an hour with aqueous potassium hydroxide (2 g. in 10 c.c.). After acidification with hydrochloric acid, the higher-melting acid separated. This is clearly the *trans*-acid, and its m. p. was depressed to 186—188° by admixture with the pure *cis*-acid. Esterification with ethereal diazomethane or with boiling methanolic hydrogen chloride gave *methyl* trans-*indane*-1 : 2-*dicarboxylate*, which formed colourless needles (from methanol), m. p. 73—74° (Found : C, 66·8; H, 6·0. $C_{12}H_{14}O_4$ requires C, 66·6; H, 6·0%).

Condensation of 4′-*Keto*-1′ : 2′ : 3′ : 4′-*tetrahydro*-2 : 3-*benzfluorene* (XIX) *with Ethyl Bromoacetate*.—A mixture of the tetracyclic ketone (XIX; Koelsch, *J. Amer. Chem. Soc.*, 1933, **55**, 3885; Lothrop and Coffman, *ibid.*, 1941, **63**, 2566) (4·7 g.), arsenic-free granulated zinc (2·6 g.) [activated as described by Fieser and Johnson (*ibid.*, 1940, **62**, 575)] ethyl bromoacetate (4·5 c.c.), and dry thiophen-free benzene (120 c.c.) was heated under reflux on the water-bath for 4 hours. After cooling, methanol (75 c.c.) was added, together with more benzene (75 c.c.). When the zinc complex had dissolved the solution was shaken with dilute hydrochloric acid, and the benzene solution was washed, dried, and then heated with phosphoric oxide for 3 hours to ensure complete dehydration of the hydroxy-ester expected as a product. The solution was then decanted, washed with water, and dried, and the solvent removed. The residue was boiled for 5 hours with ethanolic potassium hydroxide (3 g. potassium hydroxide, 25 c.c. ethanol, 5 c.c. water) in an atmosphere of nitrogen. The crude acid (3 g.) was purified through its sparingly soluble potassium salt, and the regenerated acid was crystallised from benzene and then light petroleum. The resulting unsaturated *acid* (1·4 g.) formed colourless needles, m. p. 167—168° (decomp.) (Found : C, 82·9; H, 5·6. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

We are indebted to the International Federation of University Women and the Finney–Howell Research Foundation for consecutive Fellowships which have enabled one of us (E. F. M. S.) to carry out these experiments. Micro-analyses were made by Mr. J. M. L. Cameron and Miss R. H. Kennaway.

UNIVERSITY OF GLASGOW. [*Received, August 30th*, 1948.

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182. *The Chemistry of Fungi. Part III. The Degradation of O-Dimethylcitromycin and the Structure of Citromycetin.*

By ALEXANDER ROBERTSON and W. B. WHALLEY.

The degradation of *O*-dimethylcitromycin, shown to have a reactive methylene group and to retain the essential citromycetin structure, has been studied. Hydrolytic fission of this ether gave rise to a complex mixture from which acetone, acetic acid, the ketone (I; R = Me), the acid (I; R = OH), and a substance which may be 5 : 6-dimethoxy-3-acetyldihydrocoumarin (XIII) have been isolated. Oxidation of *O*-dimethylcitromycin with ozone furnished a ketone, *O*-dimethylcitromycinone, together with considerable amounts of a compound which appears to be the corresponding alcohol *O*-dimethylcitromycinol and gives the ketone on oxidation; the same ketone is formed by oxidation with chromic acid. On hydrolysis, *O*-dimethylcitromycinone gave rise to acetone, acetic acid, the ketone (I; R = Me), the acid (I; R = OH), the 4-hydroxycoumarin (II), and the 4-hydroxy-3-acetylcoumarin (III). Formulæ (IV), (V), (VIII), and (XV; R = CO_2H) have been deduced respectively for *O*-dimethylcitromycinone, *O*-dimethylcitromycinol, *O*-dimethylcitromycin, and citromycetin.

ON being boiled with dilute sulphuric acid citromycetin, a metabolic product of various species of *Citromyces*, is converted with loss of carbon dioxide into the dihydric phenol, citromycin,

which closely resembles the parent acid and like it readily forms a dimethyl ether (Hetherington and Raistrick, *Phil. Trans.*, 1931, *B*, **220**, 209). In the course of preliminary experimental studies on the degradation and constitution of citromycetin and its dimethyl ether in these laboratories (unpublished work by one of us, A. R., and M. Tunnicliffe carried out during the period 1937—39) it became clear that, in order to avoid the complications which arise as the result of the carboxyl group originally present in citromycetin obtaining in the various degradation products, the employment of citromycin would afford a simpler experimental approach to our objective. This compound is unaffected by boiling 40% sulphuric acid or by boiling concentrated hydriodic acid. From the latter it separates as the hydriodide which, like the hydrobromide (Hetherington and Raistrick, *loc. cit.*), is readily hydrolysed by water. Although it has been found that citromycin like citromycetin is sensitive to warm alkalis, the formation of the dimethyl ether of citromycin by the methyl sulphate–sodium hydroxide method is unaccompanied by molecular change, since the use of diazomethane or of the methyl iodide–potassium carbonate method gave rise to the same dimethyl ether. Accordingly we have employed this readily accessible derivative in the present series of degradation experiments.

The application of the Zerewitinoff reaction to *O*-dimethylcitromycin gave a positive result, indicating the presence of one active hydrogen atom, but the compound did not appear to contain a hydroxyl group since it could not be induced to form any of the usual diagnostic derivatives, and we concluded that the active hydrogen indicated by the Zerewitinoff reagent was in all probability due to a reactive methylene group. The failure of *O*-dimethylcitromycin to yield products with the usual carbonyl reagents clearly indicates the absence of a normal ketonic group, a conclusion which is supported by the fact that Clemmensen reduction gave intractable resins whilst reductive acetylation furnished only unchanged material. *O*-Dimethylcitromycin does not contain a lactone group, but, like methyl *O*-dimethylcitromycetin (Hetherington and Raistrick, *loc. cit.*), it has been found to be unstable in boiling alcoholic alkalis, and accordingly its hydrolytic fission has been studied under a variety of conditions. It has been established, *inter alia*, that when *O*-dimethylcitromycin is boiled with alcoholic potassium hydroxide a mixture of acetone, acetic acid, 2-hydroxy-4 : 5-dimethoxyacetophenone (I; R = Me), and 2-hydroxy-4 : 5-dimethoxybenzoic acid (I; R = OH) is obtained, whilst when boiling saturated aqueous barium hydroxide is employed the same products are obtained together with a more complex carbonyl derivative which we have so far been able to isolate only as its 2 : 4-*dinitrophenylhydrazone*, m. p. 282° (decomp.). The nature of this substance has not been completely established but, on the basis of the empirical formula of the 2 : 4-dinitrophenylhydrazone and the further degradations of *O*-dimethylcitromycin described in this paper, we are inclined to the view that the parent ketonic product is 6 : 7-dimethoxy-3-acetyldihydrocoumarin (XIII). In spite of a careful search in the course of a considerable number of experiments on the hydrolysis of *O*-dimethylcitromycin by means of alkalis under a variety of conditions, we failed to find any evidence of the formation of the compound $C_{10}H_6O_3(OMe)_2$, m. p. 177—180°, which was obtained (in poor yield) by the hydrolytic fission of methyl *O*-dimethylcitromycetin according to the procedure of Hetherington and Raistrick (*loc. cit.*), and for which these authors suggested possible pyrone structures. Although we have not a direct proof we are inclined to the view that this compound, which is invariably obtained only in small yield from methyl *O*-dimethylcitromycetin, is an artefact formed in the course of the alkaline degradation, and further, that the carbomethoxy-group is probably involved in its formation (cf. Part II, *loc. cit.*). Since *O*-dimethylcitromycin is not hydrogenated with hydrogen and an active palladium–charcoal catalyst and is not oxidised with perbenzoic acid under the usual conditions it seems reasonably certain that it does not contain a reactive double bond. Attempts to dehydrogenate *O*-dimethylcitromycin with a palladium–charcoal catalyst or with chloranil under a variety of conditions were unsuccessful, whilst oxidation in acetone with aqueous permanganate appeared to be difficult to control and gave only a small yield of a product, m. p. 246°, which has not been further investigated. On the other hand oxidation of *O*-dimethylcitromycin with chromic acid in acetic acid furnished a ketonic substance, $C_{13}H_6O_4(OMe)_2$, m. p. 316° (decomp.), in satisfactory yield, which we have named O-*dimethylcitromycinone* and which forms an *oxime*, m. p. 268° (decomp.), a *phenylhydrazone*, and a condensation product with aniline in warm alcohol or acetic acid. The last substance appears to have the composition of an *anil* of a hydrated *O*-dimethylcitromycinone, and on being gently warmed with concentrated sulphuric acid regenerates the parent ketone. In the preparation of the oxime, m. p. 268° (decomp.), by the sodium acetate method, there is formed a small amount of a second derivative, m. p. 212° (decomp.), which is the sole product when the oximation is carried out by the pyridine procedure. Since it was converted into the oxime, m. p. 268°

(decomp.), by solution in dilute aqueous sodium hydroxide followed by acidification with acid this compound at first seemed to be an isomeride (*cis–trans* type), but the analytical results, which clearly exclude this possibility, indicate that it may be a dioxime. In the course of experiments primarily designed to detect the presence of a double bond in *O*-dimethylcitromycin it was found that the action of ozone on this compound also gave rise to a good yield of *O*-dimethylcitromycinone together with a second oxidation product $C_{13}H_8O_4(OMe)_2$, m. p. 251—252°, which we have designated O-*dimethylcitromycinol*, and which on further oxidation with chromic acid in acetic acid furnished *O*-dimethylcitromycinone. The proportion of the two compounds in the crude ozonolysis product seems to vary somewhat according to the conditions employed, but in most experiments they appeared to be produced in almost equal quantities. Since *O*-dimethylcitromycinol and *O*-dimethylcitromycinone can be isolated directly from the ozonolysis mixture when the procedure is carried out in anhydrous solvents without treating the reaction mixture with water, it seems clear that these compounds are formed by direct oxidation without the formation of an intermediate ozonide, presumably according to the scheme, $\cdot CH_2 \longrightarrow \cdot CH(OH) \longrightarrow \cdot CO$. In addition to the two main oxidation products the crude ozonolysis mixture invariably contained small amounts of material which appeared to be an ozonide and was removed by triturating the crude reaction mixture with water. When the aqueous liquor was treated with 2 : 4-dinitrophenylhydrazine hydrochloride solution a complex mixture was obtained from which the 2 : 4-*dinitrophenylhydrazone*, m. p. 236° (decomp.), of a substance was isolated, identical with a 2 : 4-dinitrophenylhydrazone subsequently obtained from the mixed product formed by the hydrolysis of *O*-dimethylcitromycinone with alkalis.

In view of the abnormal results obtained with ozone and because of the detection of active hydrogen in *O*-dimethylcitromycin in the absence of a hydroxyl group, further experiments to test for the presence of a reactive methylene group were carried out. It was found that *O*-dimethylcitromycin reacts slowly with nitrous acid to give a substance which is not identical or isomeric with either of the oximation products. This result indicates that the reactive methylene group which is readily oxidised to a carbonyl is not in the α-position to a normal reactive ketonic group, *i.e.*, $\cdot CH_2 \cdot CO \cdot$ is not converted into $\cdot C(\cdot NOH) \cdot CO \cdot$. Similarly, it was found that *O*-dimethylcitromycin condensed with piperonal in the presence of alcoholic sodium ethoxide, giving rise to a *styryl* derivative. From the fact that this compound does not appear to contain a *C*-methyl group whereas the parent ether as well as *O*-dimethylcitromycinone each contain one *C*-methyl group according to the Kuhn–Roth method of estimation, it would seem clear that a reactive methyl group and not the methylene group oxidisable to carbonyl is concerned in the formation of the styryl compound, *i.e.*, the system $CH_3 \cdot CO \cdot$ or, in view of the nitrosation results, more likely $CH_3 \cdot C{:}C \cdot CO \cdot$ is present. Curiously enough, styryl derivatives were not obtained from *O*-dimethylcitromycin when piperonal was replaced by other aromatic aldehydes, *e.g.*, benzaldehyde or *p*-dimethylaminobenzaldehyde, but whether this is significant we are unable to say at present.

O-Dimethylcitromycinone has been found to be readily decomposed both by warm alkalis and (much less readily) by warm acids. With the former agents a complex mixture is obtained, the composition of which depends to a considerable extent on the conditions employed. Thus with warm aqueous sodium hydroxide, *O*-dimethylcitromycinone gives rise to a mixture of acetone, acetic acid, the 2-hydroxy-4 : 5-dimethoxyacetophenone (I; R = Me), 2-hydroxy-4 : 5-dimethoxybenzoic acid (I; R = OH), and small amounts of two products which have been isolated as their 2 : 4-dinitrophenylhydrazones, m. p. 236° (decomp.) and m. p. 220° (decomp.), respectively. The former 2 : 4-dinitrophenylhydrazone is identical with that obtained in small yield from the crude ozonolysis mixture. The second appears to be the 2 : 4-*dinitrophenylhydrazone* of a compound $C_{11}H_6O_4(OMe)_2$. When the hot aqueous sodium hydroxide is replaced by boiling aqueous barium hydroxide the main product of the reaction, apart from acetone and acetic acid, appeared to be 4-hydroxy-6 : 7-dimethoxycoumarin (II), which was invariably accompanied by a small amount of the ketone (I; R = Me).

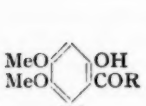
Decomposition of *O*-dimethylcitromycinone with warm concentrated hydrochloric acid gave rise to the product $C_{11}H_6O_4(OMe)_2$, m. p. 208°, which we consider to be 4-*hydroxy*-6 : 7-*dimethoxy*-3-*acetylcoumarin* (III) and which gives the 2 : 4-dinitrophenylhydrazone, m. p. 220° (decomp.), identical with that separated from the sodium hydroxide hydrolysate. Together with this compound there are formed carbon dioxide and small amounts of the substance giving the 2 : 4-dinitrophenylhydrazone, m. p. 236° (decomp.), but the presence of acetone in the hydrolysate has not been detected. When hydrochloric acid was replaced by 40% sulphuric acid, *O*-dimethylcitromycinone appeared to form a sparingly soluble sulphate which did not

undergo decomposition. A more detailed examination of the acidic decomposition of *O*-dimethylcitromycinone will be made when sufficient material is available. Although it has not yet been possible to synthesise 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (III) (cf. Part II, this vol., p. 562) in order to make a direct comparison with the natural degradation product, m. p. 208°, we consider that the structure of this compound follows from the fact that like 4-hydroxy-3-acetylcoumarin (Part II, *loc. cit.*) it forms a 2 : 4-dinitrophenylhydrazone, and on alkaline hydrolysis gives rise to the expected decomposition products, *viz.*, acetone, acetic acid, the ketone (I; R = Me), the acid (I; R = OH) and 4-hydroxy-6 : 7-dimethoxycoumarin (II). In support of the view that the coumarin, m. p. 208°, contains a *C*-acetyl group, it may be noted that in general the carbonyl group enolising to give the hydroxyl group in the 4-position of 4-hydroxycoumarins does not normally react with hydrazines. The degradation product (III) has been found to be isomeric and not identical with the synthetical substance believed to be 6 : 7-dimethoxy-2-methylchromone-3-carboxylic acid (Part II, *loc. cit.*), but in the course of experiments on the synthesis of the latter compound by the condensation of the ketone (I; R = CH_2·CO·CH_3) with ethyl carbonate by means of sodium, a method which can conceivably give rise to coumarin or chromone, it was found in two experiments that, together with the chromone, a small amount of a compound was formed which gave a 2 : 4-dinitrophenylhydrazone, m. p. 220° (decomp.), identical with that from *O*-dimethylcitromycinone.

If the assumption is made, which appears reasonable, that the hydrolysis of *O*-dimethylcitromycinone under the conditions discussed is not preceded by a deep-seated isomeric change in the parent molecular structure, then, from the formation of the various hydrolytic products—acetone, acetic acid (I; R = Me), (I; R = OH), (II), and (III), which have been defined, it seems fairly certain that *O*-dimethylcitromycinone is best represented by formula (IV). Formula (VII) is considered to be much less likely, whilst structures of the type (XII), which cannot give rise to 4-hydroxy-6 : 7-dimethoxycoumarin or its derivatives, can be excluded. The structure type (VI), or a variation of it, for *O*-dimethylcitromycinone, which could conceivably arise by the oxidation of an active methyl group, is excluded because the compound retains the *C*-methyl group originally present in *O*-dimethylcitromycin. Though a substance having a formula of the type (IV) might not on general grounds be expected readily to form ketonic derivatives, the instability of the chromono-γ-pyrone system in (IV) towards warm hydrochloric acid is more readily understood. The latter property is regarded as being due to the presence of the ether link involving the oxygen atom of the enolic form of the potential carboxyl group, *i.e.*, due to the tendency to regenerate the 4-hydroxycoumarin system by fission as indicated by the dotted line in formula (IV). The possibility that the degradation of *O*-dimethylcitromycinone with acids is initiated by hydration to give the intermediate (XIV) is considered unlikely. On the other hand, the main objection to formula (VII) for *O*-dimethylcitromycinone is that a substance having this structure, which could conceivably arise by the isomerisation of a compound having formula (IV), would hardly be expected to be sensitive to the hydrolytic effects of warm acids, and would certainly be less likely to form ketonic derivatives than (IV). The chemistry of *O*-dimethylcitromycinol, the oxidation product intermediate between *O*-dimethylcitromycin and *O*-dimethylcitromycinone, has not yet been fully investigated, but on the basis of the structure (IV) for the ketonic compound it seems clear that *O*-dimethylcitromycinol is best represented by formula (V). This implies that the compound is a 4-carbinol base comparable to the xanth-hydrols and consequently would be expected to react with acids, forming salts of the pyrylium type with the elimination of water. In agreement with this, a well-defined picrate, a perchlorate, and a ferrichloride have been prepared from the base (private communication from Mr. G. W. K. Cavill of this laboratory).

It is clear that *O*-dimethylcitromycin contains a reactive methylene group which is readily oxidised to give a reactive carbonyl group and further, that it contains a reactive methyl group which condenses with piperonal to give the styryl derivative. Thus on the basis of the two most probable formulæ, (IV) and (VII), for *O*-dimethylcitromycinone, *O*-dimethylcitromycin may be formulated as (VIII), type (IX), type (X), or type (XI), and of these the structures type (IX) and type (XI), which contain a γ-pyran nucleus (or the possible isomeric forms containing an α-pyran nucleus), may be excluded because in substances having this kind of residue the double bond reacts normally, undergoing hydrogenation and oxidation in the usual manner. Of the two remaining feasible structures (VIII) and (X) for *O*-dimethylcitromycin we prefer (VIII) in which the reactivity of the methylene group in the 4-position of the chromeno-residue is reminiscent of that in indene, fluorene, or xanthen, which is readily oxidised to a carbonyl group and responds to the Zerewitinoff reagent (one active hydrogen). Further we do not regard the angular structure, type (X), as being an attractive alternative to (VIII) because on

general grounds we would not expect the methylene group of the system $\cdot O\cdot CH_2\cdot C:$ to be reactive, and in support of this conclusion we have found in analogous chromeno(3′ : 4′ : 4 : 3)coumarins (Robertson, *et al.*, *J.*, 1936, 423) that the $\cdot O\cdot CH_2\cdot$ group in the chromeno-system is not oxidised by ozone to $\cdot O\cdot CO\cdot$, *i.e.*, the chromen residue is not converted into a coumarin residue. On the basis of the formula suggested it would seem that the comparatively ready formation of the ketone (I; R = Me) and the acid (I; R = OH) in the course of the hydrolytic fission of *O*-dimethylcitromycin with aqueous alkalis is due to the oxidative action of these reagents on the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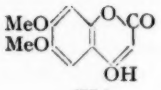
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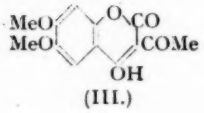
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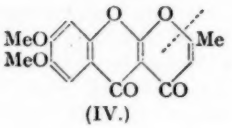
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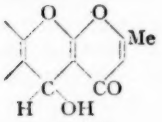
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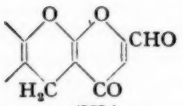
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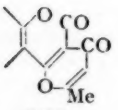
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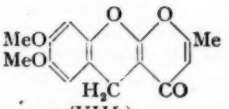
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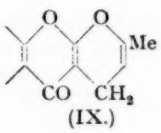
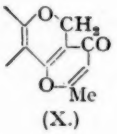
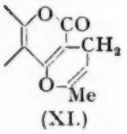

(IX.)


(X.)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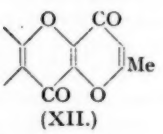
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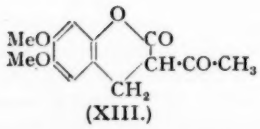
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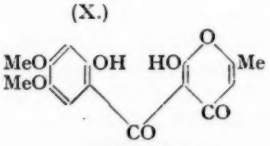
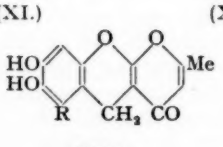
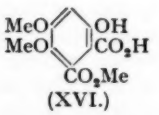

(XIV.)


(XV.)


(XVI.)

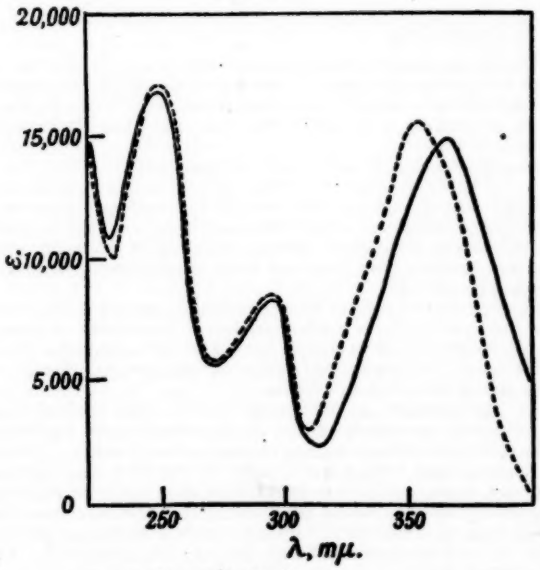
reactive methylene group. If the suggestion can be substantiated that the product obtained as its 2 : 4-dinitrophenylhydrazone, m. p. 282° (decomp.), from the hydrolysis of *O*-dimethylcitromycin by means of boiling aqueous barium hydroxide is the dihydrocoumarin derivative (XIII), then decisive evidence will be available in favour of formula (VIII) for *O*-dimethylcitromycin. Meanwhile, the spectroscopic evidence, as reported by Dr. Stubbs in the addendum, clearly supports the structure (VIII) for *O*-dimethylcitromycin, where the methylene group and the oxygen atom act as insulators between the chromophoric phenyl group and the γ-pyrone residue.

From the structure (VIII) allocated to its dimethyl ether citromycin is clearly represented by formula (XV; R = H). It has been assumed that the parent compound citromycetin is a carboxycitromycin (cf. Hetherington and Raistrick, *loc. cit.*), a conclusion which does not necessarily follow since the conversion of citromycetin into citromycin by means of warm dilute sulphuric acid may well involve a fundamental change in the original citromycetin structure simultaneous with the loss of carbon dioxide, and, further, the carboxyl group originally present may not be that ultimately eliminated. Accordingly, we have endeavoured to obtain evidence on this point. Although it was not found possible to decarboxylate *O*-dimethylcitromycetin by standard procedures, citromycetin is smoothly converted into citromycin in hot glycerol. Further, alkaline degradation of *O*-dimethylcitromycetin invariably gives rise, *inter alia*, to 3-hydroxy-5 : 6-dimethoxyphthalic acid, whereas from *O*-dimethylcitromycin the only phenolic acid obtained is 2-hydroxy-4 : 5-dimethoxybenzoic acid, indicating that the carboxyl group lost in the decarboxylation process is that appearing in the 1-position of the phthalic acid. Moreover, it has been found that the oxidation of methyl *O*-dimethylcitromycetin with aqueous potassium permanganate in acetone gives rise to an *acid-ester* (XVI) of 3-hydroxy-5 : 6-dimethoxyphthalic acid, a result which serves to prove that the carbomethoxy-group in methyl *O*-dimethylcitromycetin is present in the hydroxyquinol residue. These results, together with the spectroscopic evidence obtained by Dr. A. L. Stubbs (see addendum), confirm the view that the conversion of citromycetin into citromycin is a simple decarboxylation. Consequently citromycetin is represented by formula (XV; R = CO_2H).

In the course of attempts to hydrogenate *O*-dimethylcitromycinone dissolved in dioxan by

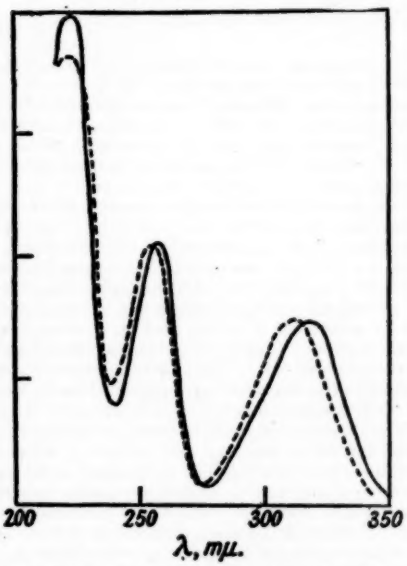
means of hydrogen and a palladium–charcoal catalyst, it was found that hydrogen was not absorbed but a product was obtained which appeared to be a *hydrate*, $C_{13}H_8O_5(OMe)_2$, of the original substance. Subsequently, it was discovered that the hydrate was formed by the catalyst in the absence of hydrogen and in the presence of a trace of hydrochloric acid. This hydrate, which gives a ferric reaction and is readily soluble in aqueous sodium hydroxide, regenerates *O*-dimethylcitromycinone on treatment with cold sulphuric acid or warm acetic anhydride, gives the same anil as *O*-dimethylcitromycinone, and on oximation furnishes the oxime of *O*-dimethylcitromycinone. On hydrolysis with warm 2N-sodium hydroxide the hydrate gave rise to acetone, the ketone (I; R = Me), and 4-hydroxy-6 : 7-dimethoxycoumarin, whilst on ozonolysis it gave rise to a complex mixture which has not been fully investigated but from which the 2 : 4-dinitrophenylhydrazone, m. p. 236°, has been obtained, identical with that formed by material from the alkaline hydrolysis of *O*-dimethylcitromycinone. In the meantime, we assign formula type (XIV) provisionally to this hydrate.

FIG. 1.



——— O-*Dimethylcitromycin.*
– – – – – *Methyl* O-*dimethylcitromycetin.*

FIG. 2.



——— 2-*Hydroxy-4* : 5-*dimethoxybenzoic acid.*
– – – – – 2-*Hydroxy-6-carbomethoxy-4* : 5-*dimethoxybenzoic acid.*

Addendum on Ultra-violet Absorption Spectra (A. L. STUBBS).—The ultra-violet absorption spectra of *O*-dimethylcitromycin (VIII) and methyl *O*-dimethylcitromycetin (XV; R = CO_2Me and OH groups replaced by OMe) have been examined in ethanol solution, using a Hilger Medium Quartz Spectrograph in conjuction with a rotating sector photometer. The absorption curves are shown in Fig. 1, and the positions and intensities of maximum absorption are tabulated below.

Compound.	$\lambda_{max.}$ (mμ).	ε, max.	Compound.	$\lambda_{max.}$ (mμ).	ε, max.
(I, R = OH)	318	7,390	(VIII)	365	15,100
	256·5	10,600		296	8,360
	222	19,800		249	16,900
(XVI)	311	7,420	Methyl *O*-dimethylcitromycetin	354	15,600
	255·5	10,400		293	8,570
	222	19,200		250	17,000

(Solvent, ethanol.)

In order to confirm that the sole difference between the citromycin and citromycetin derivatives is in the presence or absence of the carboxyl group, the spectra of these two compounds may be compared with those of the benzoic acid (I; R = OH) and its carbomethoxy-derivative (XVI), also measured in ethanol solution (Fig. 2 and Table). The elimination of the carbomethoxy-group in both pairs of compounds results in entirely analogous spectral changes,

which are in fact extremely small, and make it certain that no other structural change has taken place during the decarboxylation of the citromycetin compound.

It is interesting to discuss the spectra briefly in terms of chromophoric groups. The phenyl chromophore in (VIII) is " insulated " by the oxygen atom and the methylene group from the rest of the molecule. Consequently the characteristic absorption maxima of (I; R = OH) should appear with little change. It is therefore justifiable to associate the 318 mμ and 256·5 mμ maxima of (I; R = OH) with the 296 mμ and 249 mμ maxima of (VIII), the slight shift to shorter wave-lengths resulting from the replacements of carbonyl by methylene group. The 365 mμ maximum of (VIII) is, on this basis, to be ascribed to the remaining unsaturated linkages in the molecule, which chromophorically may be compared with phorone $CMe_2{:}CH{\cdot}CO{\cdot}CH{:}CMe_2$. Phorone shows $\lambda_{max.}$ 263 and 357 mμ with molecular extinction coefficient 23,500 and 82 respectively. The similarity in the positions of the 357 mμ maximum of phorone and the 365 mμ maximum of (VIII) justifies the analogy, but the ring closure and substitution have clearly given rise to considerable increase in extinction. Such an increase in extinction for a low intensity band, located in the carbonyl group, is not unusual (cf. Morton and Rosney, *J.*, 1926, 706).

Experimental.

Citromycin.—(*a*) A mixture of citromycetin (3 g.), water (180 ml.), and sulphuric acid (30 ml.) was boiled under reflux for 8 hours and then diluted with water (100 ml.). Next day the crystalline precipitate was collected, triturated with aqueous sodium hydrogen carbonate, and crystallised from dilute methanol, giving citromycin (2·2 g.) in pale greenish yellow needles, m. p. 296—298° (decomp.) (cf. Hetherington and Raistrick, *loc. cit.*, who give m. p. 285—290°).

(*b*) When a mixture of citromycetin (0·8 g.), glycerol (5 ml.), and copper bronze (0·3 g.) in an atmosphere of nitrogen was gradually heated (oil-bath) to 280° and then kept at this temperature for 10 minutes carbon dioxide was steadily evolved. The cooled mixture was diluted with aqueous sodium hydrogen carbonate, the precipitate was repeatedly extracted with boiling alcohol, and the combined extracts were concentrated. On cooling, the residue deposited citromycin in pale greenish yellow needles (0·1 g.), m. p. 298° (decomp.) after recrystallisation, identical with a specimen prepared by method (*a*) and giving *O*-dimethylcitromycin on methylation.

A mixture of citromycin (0·5 g.) and hydriodic acid (25 ml., of constant-boiling mixture) was boiled under reflux for 3 hours, and on cooling gave the hydriodide in golden needles. Treatment of this salt with aqueous sodium hydrogen carbonate regenerated citromycin, identified by comparison with authentic material. Similarly, citromycin was recovered unchanged when red phosphorus (0·2 g.) was added to the reaction mixture and the time of heating extended to 4 hours.

O-*Dimethylcitromycin.*—Citromycin (10 g.) was methylated by being heated with methyl iodide (20 ml.) and acetone (1000 ml.) containing potassium carbonate (40 g.) on the steam-bath for 6 hours until the ferric reaction was negative, with the addition of more iodide (10 ml.) after 3 hours. The hot solution was filtered, the potassium salts extracted with boiling acetone (2 × 100 ml.), the combined filtrates evaporated, and the residue crystallised from methyl or ethyl alcohol. After having been thoroughly extracted with water to remove traces of potassium salts, the dimethyl ether was recrystallised from methanol, forming colourless prisms (9 g.), m. p. 225—227°, identical with a specimen prepared by diazomethane (Hetherington and Raistrick, *loc. cit.*) [Found: C, 65·6; H, 5·3; *C*-methyl, 6·1. Calc. for $C_{12}H_5O_3(OMe)_3(Me)$: C, 65·7; H, 5·2; *C*-methyl, 5·2%].

When a mixture of *O*-dimethylcitromycin (0·2 g.), piperonal (0·2 g.), potassium ethoxide (from 0·05 g. of potassium), and alcohol (7 ml.) was heated on the water-bath for ½ hour and then kept at room temperature for 7 days, the *styryl* derivative gradually separated in clusters of pale greenish yellow needles (0·1 g.) which on isolation and recrystallisation from alcohol had m. p. 243° (Found: C, 67·5; H, 4·5. $C_{23}H_{18}O_7$ requires C, 68·0; H, 4·4%). When piperonal was replaced by benzaldehyde or by *p*-dimethylaminobenzaldehyde condensation did not take place.

A mixture of *O*-dimethylcitromycin (0·2 g.), alcohol (5 ml.), and concentrated hydrochloric acid (3 ml.) was cooled to 0°, treated with amyl nitrite (3 ml.), and then kept at room temperature for 4 days. On the addition of water to the clear solution an *iso*nitroso-derivative (0·2 g.) gradually separated, and on recrystallisation from aqueous alcohol formed almost colourless needles, m. p. 259—260° (Found: C, 61·9, 62·0; H, 5·3, 5·1. N, 4·4. Calc. for $C_{15}H_{13}O_6N$: C, 59·4; H, 4·3; N, 4·6%).

Hydrolysis of O-*Dimethylcitromycin with Potassium Hydroxide.*—(*a*) A mixture of *O*-dimethylcitromycin (2 g.), alcohol (16 ml.), and potassium hydroxide (4 g., dissolved in 7 ml. of water) was kept at 100° for 3½ hours, and simultaneously a slow stream of nitrogen was led through the containing vessel and the effluent gas was passed through a wash-bottle containing aqueous 2 : 4-dinitrophenylhydrazine sulphate. When the mixture had cooled, the yellow precipitate, which had formed in the wash-bottle, was separated, washed, and crystallised from methanol, giving the 2 : 4-dinitrophenylhydrazone of acetone in yellow needles, m. p. 125°, identified by comparison with an authentic specimen. The alkaline hydrolysate was diluted with water (50 ml.), the greater part of the alcohol was evaporated in a vacuum, the residual solution was saturated with carbon dioxide and extracted with chloroform (50 ml. × 4), and the dried chloroform extracts were distilled, leaving an intractable gum (0·6 g.). After acidification with 2N-sulphuric acid the residual aqueous liquor was extracted with ether (6 × 120 ml.), the combined extracts dried and evaporated, and the residue crystallised from aqueous acetone, giving 2-hydroxy-4 : 5-dimethoxybenzoic acid in colourless needles (0·35 g.), m. p. 213—214° (decomp.), which had a blue ferric reaction and were identified by comparison with an authentic specimen (Head and Robertson, *J.*, 1931, 2432) [Found: C, 54·6; H, 5·0; OMe, 31·2. Calc. for $C_7H_4O_3(OMe)_3$: C, 54·5; H, 5·1; OMe, 31·3%].

(*b*) The foregoing degradation was repeated with *O*-dimethylcitromycin (1 g.), and the cooled hydrolysate was acidified immediately with 2N-sulphuric acid, filtered to remove a gummy precipitate (X), and treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate solution. Next day the precipitate (0·4 g.) was collected, dried, dissolved in benzene, and chromatographed on a column of aluminium oxide, giving two main zones and with several minor ones. The lower main pale yellow zone (A) was washed through the column with benzene and then the main deep red zone (B) was washed through with chloroform. Evaporation of the benzene liquor containing material from zone (A) left the 2 : 4-dinitrophenylhydrazone of acetone, forming yellow needles, m. p. 125°, from methanol, undepressed on admixture with an authentic specimen. The residue obtained from the evaporation of the chloroform liquor containing the material from zone (B) was crystallised from benzene and then chloroform giving the 2 : 4-dinitrophenylhydrazone of 2-hydroxy-4 : 5-dimethoxyacetophenone, in red needles, m. p. 228° (decomp.), identified by comparison with an authentic specimen (Part II, *loc. cit.*) [Found : C, 51·5; H, 4·4; N, 13·5; OMe, 17·4. Calc. for $C_{14}H_{10}O_5N_4(OMe)_2$: C, 51·1; H, 4·3; N, 14·9; OMe, 16·5%]. Distillation of the acidic filtrate left after the removal of the 2 : 4-dinitrophenylhydrazones gave acetic acid which was isolated as the sodium salt and identified by conversion into the anilide, m. p. 112°, after purification, undepressed on admixture with an authentic sample (Found : N, 10·7. Calc. for C_8H_9ON : N, 10·4%).

On repeated crystallisation from methanol the precipitate (X) gave 2-hydroxy-4 : 5-dimethoxyacetophenone (10 mg.) in colourless stout prisms, m. p. 112°, identified by comparison with synthetical material (Part II, *loc. cit.*).

(*c*) *O*-Dimethylcitromycin (5 g.) was hydrolysed by being boiled with potassium hydroxide (10 g.), water (10 ml.), and alcohol (40 ml.) in an atmosphere of nitrogen during 3½ hours according to the procedure employed by Hetherington and Raistrick (*loc. cit.*) for *O*-dimethylcitromycetin. The effluent gas contained acetone which was isolated as the 2 : 4-dinitrophenylhydrazone, m. p. 125°, after purification. The dark alkaline hydrolysate was diluted with water (100 ml.), the greater part of the alcohol removed under reduced pressure, and the residual liquor saturated with carbon dioxide and extracted with chloroform (5 × 50 ml.). Crystallisation of the residue left on evaporation of the dried chloroform extracts from methanol gave 2-hydroxy-4 : 5-dimethoxyacetophenone (25 mg.), m. p. 112°, identical with an authentic sample.

After having been extracted with chloroform the aqueous liquor was acidified with dilute sulphuric acid and found to contain acetic acid in addition to small amounts of acetone and 2-hydroxy-4 : 5-dimethoxyacetophenone which were identified by treating a portion of the acidic liquor with 2 : 4-dinitrophenylhydrazine sulphate and separating the resulting mixed hydrazones by chromatography.

In spite of a careful search on the occasion of a number of experiments we failed to find any trace of the so-called pyrone, $C_{10}H_4O_3(OMe)_2$, which was isolated from *O*-dimethylcitromycetin by Hetherington and Raistrick (*loc. cit.*).

(*d*) A saturated solution of barium hydroxide (100 c.c.), containing a suspension of the *O*-dimethylcitromycin (1 g.), was refluxed in an atmosphere of nitrogen for 25 minutes, and half of the cooled solution was acidified with sulphuric acid, filtered, and distilled, giving an aqueous distillate which contained acetic acid, identified by conversion into the anilide. The remaining half of the barium hydroxide liquor was acidified with hydrochloric acid, and filtered to remove an intractable solid (0·5 g.) which constitutes the bulk of the product, and the filtrate was treated with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride. A solution of the resulting precipitate (0·3 g.) in benzene was poured on a column of aluminium oxide giving (1) an orange yellow zone which was washed through the column with benzene, (2) a deep red zone which was washed through with chloroform, and (3) two smaller brownish zones which were eluted with chloroform and gave only resinous material. The product from zone (1) consisted of acetone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 125°, and that from zone (2) was obtained as a bright crimson solid on evaporation of the chloroform and on crystallisation from ethyl acetate gave a *compound* in fluffy crimson needles, m. p. 282° (decomp.), which appeared to be a 2 : 4-dinitrophenylhydrazone of a compound $C_{11}H_8O_3(OMe)_2$ [Found : C, 53·0; H, 4·5; N, 13·1; OMe, 11·3. $C_{17}H_{12}O_6N_4(OMe)_2$ requires C, 53·0; H, 4·2; N, 13·0; OMe, 14·4%].

The effluent gas contained acetone which was isolated as the 2 : 4-dinitrophenylhydrazone (0·6 g.). In some experiments 2-hydroxy-4 : 5-dimethoxyacetophenone and 2-hydroxy-4 : 5-dimethoxybenzoic acid were also obtained.

Ozonolysis of O-Dimethylcitromycin.—Of many experiments carried out the following is typical. A moderate stream of dry ozone and oxygen was bubbled through a solution of the dimethyl ether (1 g.) in anhydrous chloroform (75 ml.) kept at 0° for 20 minutes, the chloroform was removed under reduced pressure, and the residue was triturated with water (150 ml.). Next day the solid was collected and refluxed with alcohol (125 ml.), the cooled solution kept for 24 hours, and the crystalline solid collected and recrystallised from much alcohol or dioxan or a small volume of glacial acetic acid, giving O-*dimethylcitromycinone* in very pale fawn needles (0·5 g.), m. p. 316° (decomp.) [Found : (mean of 4 carbon and hydrogen determinations) : C, 62·6; H, 4·4; OMe, 21·0; *C*-Me, 7·5. $C_{12}H_2O_4(OMe)_3(Me)$ requires C, 62·5; H, 4·2; OMe, 21·5; *C*-Me, 5·2%]. This compound has a negative ferric reaction, is insoluble in aqueous sodium hydroxide, sparingly soluble in the usual organic solvents, and forms a yellow solution in concentrated hydrochloric acid. A mixture of *O*-dimethylcitromycinone (0·25 g.), hydroxylamine hydrochloride (0·1 g.), sodium acetate (0·1 g.), and alcohol (25 ml.) was refluxed on the steam-bath for 6 hours; on cooling the clear solution deposited the *oxime* (0·2 g.) in pale greenish needles, which on recrystallisation from alcohol had m. p. 268° (decomp.) and had a negative ferric reaction (Found : C, 59·5; H, 4·1; N, 5·0. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3; N, 4·7%). In some experiments a second and more soluble product of oximation, m. p. 212° (decomp.), was obtained from the alcohol residues. This substance appeared to be the sole reaction product when the oximation was carried out in pyridine. A mixture of *O*-dimethylcitromycinone (0·5 g.), hydroxylamine hydrochloride (0·25 g.), and pyridine (5 ml.) was warmed on the steam-bath and the clear solution, which was obtained in the course of a few minutes, poured into excess of dilute hydrochloric acid. Crystallisation of the well washed precipitate from alcohol gave the *compound* in colourless needles (0·5 g.), m. p. 212° (decomp.),

having a negative ferric reaction (Found : C, 56·5; H, 4·0; N, 9·3. $C_{15}H_{14}O_6N_2$ requires C, 56·6; H, 4·4; N, 9·0%).

When this substance was dissolved in excess of 2N-sodium hydroxide and the solution acidified with hydrochloric acid, the oxime of *O*-dimethylcitromycinone, m. p. 268° (decomp.) after purification, was obtained in quantitative yield.

A mixture of *O*-dimethylcitromycinone (0·5 g.), phenylhydrazine hydrochloride (0·5 g.), sodium acetate (0·5 g.), and alcohol (25 ml.) was warmed on the steam-bath until a clear solution was obtained, and then a part of the solvent was evaporated. On cooling, the residual solution deposited the *phenylhydrazone* (0·5 g.) which, on recrystallisation from alcohol, formed colourless needles, m. p. 218° (Found : N, 6·8. $C_{21}H_{18}O_5N_2$ requires N, 7·4%).

When a mixture of *O*-dimethylcitromycinone (1 g.), aniline (3 ml.), and acetic acid (10 ml.) was warmed on the water-bath for 1 minute a bright yellow crystalline mass gradually separated. Recrystallisation of this from dioxan, chloroform, or acetic acid gave the *anil* of hydrated *O*-dimethylcitromycinone in bright yellow prisms, m. p. 252° (decomp.), sparingly soluble in alcohol, ethyl acetate, or chloroform (Found : C, 66·4; H, 5·0; N, 3·6. $C_{21}H_{19}O_6N$ requires C, 66·1; H, 5·0; N, 3·7%). The same compound was obtained when the reaction was carried out in boiling alcohol during 8 hours. When a solution of this product in a little concentrated sulphuric acid was warmed on the water-bath for 3 minutes, cooled, and poured into water, a precipitate of *O*-dimethylcitromycinone separated, m. p. 316° (decomp.), after purification.

Evaporation under reduced pressure of the alcoholic liquor left after the separation of the crude *O*-dimethylcitromycinone a viscous residue which was dissolved in hot dioxan (10 ml.). On cooling, the solution slowly deposited O-*dimethylcitromycinol* which then crystallised from acetone, alcohol, or dioxan, forming almost colourless needles, m. p. 251—252° (decomp.) [Found : C, 61·8; 62·3; H, 4·7, 5·0; OMe, 22·9; *C*-Me, 6·3. $C_{12}H_5O_4(OMe)_3(Me)$ requires C, 62·1; H, 4·8; OMe, 21·4; *C*-Me, 5·2%]. This compound dissolves in warm aqueous sodium hydroxide, has a negative ferric reaction, forms a bright yellow solution in concentrated hydrochloric acid, and does not form ketonic derivatives. A mixture of *O*-dimethylcitromycinol (0·3 g.), chromic anhydride (0·3 g.), and acetic acid (3 ml.) was boiled under reflux for 5 minutes and, on being cooled, deposited *O*-dimethylcitromycinone (0·2 g.) which had m. p. 316° (decomp.) after purification from acetic acid and was identical with an authentic specimen.

The aqueous extract of the crude ozonolysis product, which was only faintly acid and did not contain a detectable amount of volatile acid, gave a precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate of which 0·8 g. was collected from 4 g. of *O*-dimethylcitromycetin. A solution of this material in chloroform was chromatographed on a column of aluminium oxide, giving four zones : (1) deep red, washed through the column with chloroform, (2) pale orange yellow, washed through with chloroform, (3) orange, washed through with a chloroform–methanol mixture (9 : 1), (4) deep red, washed through with methanol. Evaporation of the extracts from zones (1), (3), and (4) each gave resinous material which has not yet been further examined, whilst the elution of the material forming zone (2) with chloroform provided an orange crystalline solid (0·4 g.). Recrystallisation of this from chloroform or ethyl acetate gave a product in orange needles, m. p. 236° (decomp.), which appeared to be a 2 : 4-dinitrophenylhydrazone [Found : C, 53·4; H, 4·1; N, 13·3. OMe, 12·6. Calc. for $C_{17}H_{12}O_6N_4(OMe)_2$: C, 53·0; H, 4·2; N, 13·0; OMe, 14·4. Calc. for $C_{17}H_{10}O_6N_4(OMe)_2$: C, 53·3; H, 3·7; N, 13·1; OMe, 14·5%].

In several ozonolysis experiments *O*-dimethylcitromycinone partly separated from the chloroform solution during the passage of the gases, and it was subsequently discovered that this compound and its isomeride were most conveniently obtained by evaporating the chloroform solution and extracting the residue with warm alcohol (125 ml.). Evaporation of the alcoholic extract left *O*-dimethylcitromycinol (0·4—0·5 g.), whilst the alcohol-insoluble solid was almost pure *O*-dimethylcitromycinone.

Oxidation of O-*Dimethylcitromycin with Chromic Anhydride and with Potassium Permanganate.*—Chromic anhydride (0·8 g.), dissolved in acetic acid (25 ml.), was added gradually to a solution of the dimethyl ether (0·35 g.) in the same solvent (5 ml.), and the mixture boiled for 10 minutes. On cooling, the bright green solution gradually deposited *O*-dimethylcitromycinone in pale buff coloured needles (0·2 g.), m. p. 316° (decomp.) after recrystallisation (Found : C, 62·0; H, 4·9%). This material was found to be identical with an authentic specimen, and gave rise to the oxime, m. p. and mixed m. p. 268° (decomp.).

A solution of potassium permanganate (4 g.) in water (75 ml.) was added gradually during 6 hours to *O*-dimethylcitromycin (1 g.) dissolved in acetone (300 ml.), and next day the mixture was cleared with sulphur dioxide, the greater part of the acetone was removed under reduced pressure, and the residual solution was warmed with a little 2N-sulphuric acid and extracted with ether (6 × 100 ml.). Evaporation of the dried extracts left a residue which on repeated crystallisation from acetone gave a product in rosettes of plae yellow needles (10 mg.), m. p. 246° (decomp.), having a negative ferric reaction and exhibiting a green fluorescence in acetone (Found : C, 66·9; H, 5·7; OMe, 20·4%).

Hydrolysis of O-*Dimethylcitromycinone with Alkali.*—(*a*) A mixture of the compound (0·5 g.) in 2N-sodium hydroxide (20 ml.) was heated on the steam-bath for 3—4 minutes, and the resulting solution acidified with 2N-sulphuric acid, kept for 16 hours, filtered to remove a trace of amorphous solid, and treated with excess of 2 : 4-dinitrophenylhydrazine sulphate solution. Next day the precipitate (1·75 g., from four experiments) was collected, dried, and dissolved in benzene. When this solution was poured on a column of aluminium oxide and the chromatogram developed with the same solvent, four zones were obtained : (1) a pale orange-yellow zone which was washed through with benzene, giving acetone 2 : 4-dinitrophenylhydrazone (0·2 g.), m. p. and mixed m. p. 125° (Found : N, 23·8. Calc. for $C_9H_{10}O_4N_4$: N, 23·5%), (2) a pale orange zone which was washed through with chloroform and gave a 2 : 4-dinitrophenylhydrazone, forming orange needles (0·3 g.), m. p. 236° (decomp.), from ethyl acetate, identical with the 2 : 4-dinitrophenylhydrazone obtained from the aqueous washings of the ozonolysis mixture, (3) a greenish yellow zone which was washed through the column with a chloroform–methanol mixture (9 : 1) and the product crystallised from ethyl acetate, forming orange tablets, m. p. 220°, which we consider may be the 2 : 4-dinitrophenylhydrazone of 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin,

(4) a deep red zone which was washed through the column with methanol. On evaporation of the solvent a substance was left which appeared to be a 2 : 4-dinitrophenylhydrazone (16 mg.), and crystallised from methanol in red needles, m. p. 296° (decomp.), but the amount available was insufficient for final purification and analysis.

Distillation of the aqueous liquors from the crude mixed 2 : 4-dinitrophenylhydrazones gave acetic acid which was identified by conversion into the anilide, m. p. and mixed m. p. 112° (Found : N, 10·7. Calc. for C_8H_9ON : N, 10·4%).

(*b*) *O*-Dimethylcitromycinone (1 g.) was heated with 2N-sodium hydroxide (65 ml.) for 15 minutes, and the cooled mixture was diluted with water (100 ml.), acidified with dilute sulphuric acid, filtered next day to remove a trace of solid, and divided into two equal portions. One portion of the solution was extracted with ether (6 × 100 ml.); the residue left on evaporation of the crude extracts was separated by means of aqueous sodium hydrogen carbonate into 2-hydroxy-4 : 5-dimethoxyacetophenone and 2-hydroxy-4 : 5-dimethoxybenzoic acid. The ketone was purified by repeated crystallisation from methanol, forming colourless prisms, m. p. and mixed m. p. 112°, identical with a synthetical specimen (Part II, *loc. cit.*). The acid separated from aqueous acetone in colourless needles, m. p. 213—214°, and was identified by comparison with synthetical material.

Addition of aqueous 2 : 4-dinitrophenylhydrazine sulphate to the second portion of the acidified hydrolysate gave an orange-red precipitate which was collected, washed, and dried. On being chromatographed from benzene on a column of aluminium oxide this was separated into the 2 : 4-dinitrophenylhydrazones of acetone and of 2-hydroxy-4 : 5-dimethoxyacetophenone which were identified by comparison with authentic specimens.

(*c*) *O*-Dimethylcitromycinone (1 g.) was boiled under reflux with saturated aqueous barium hydroxide (100 ml.) for ½ hour, and the filtered solution acidified with hydrochloric acid. After removal of a trace of solid the solution was treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate, and next day the product (0·7 g.) was collected, dried, and extracted with benzene, leaving an almost colourless residue (0·1 g.). Crystallisation of this from ethyl acetate gave 4-hydroxy-6 : 7-dimethoxycoumarin, m. p. 278° (decomp.), identified by comparison with a synthetical specimen (Part II, *loc. cit.*). Methylation of the coumarin (0·3 g.) with excess of potassium carbonate and methyl iodide in boiling acetone (20 ml.) during 2 hours gave the 4-methyl ether, forming colourless needles from methanol, m. p. 202°, identical with a synthetical specimen (Found : C, 61·0; H, 5·2. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%). Acetylation of the coumarin (0·3 g.) with acetic anhydride (5 ml.) and pyridine (5 ml.) gave the acetate, which formed prisms, m. p. 242°, from alcohol, identical with an authentic specimen (Found : C, 59·3; H, 4·8. Calc. for $C_{13}H_{12}O_6$: C, 59·1; H, 4·6%) (Part II, *loc. cit.*). Chromatography of the yellow benzene extract of the crude product gave the 2 : 4-dinitrophenylhydrazone of acetone, m. p. and mixed m. p. 125°, and the 2 : 4-dinitrophenylhydrazone of 2-hydroxy-4 : 5-dimethoxyacetophenone, m. p. and mixed m. p. 228° (decomp.).

Hydrolysis of O-*Dimethylcitromycinone with Acid.*—(*a*) A solution of the dimethyl ether (1 g.) in concentrated hydrochloric acid (50 ml.) was kept at 100° for 15 minutes, cooled, diluted with water (80 ml.), almost neutralised with 2N-sodium hydroxide, and treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate. The copious precipitates (0·9 g.) from each of four such experiments were combined and extracted with a large volume of benzene, leaving a residue of unchanged material (2 g., m. p. 316°), and the benzene extract was run through a column of aluminium oxide, giving a yellow and an orange zone. The yellow zone was washed through the column with chloroform; the product left on evaporation of the solvent was an orange solid (1·3 g.), which on recrystallisation from ethyl acetate gave a hydrazone in small orange yellow needles, m. p. 236° (decomp.), identical with the 2 : 4-dinitrophenylhydrazone, m. p. 236° (decomp.), obtained from the aqueous extract of the crude ozonolysis product from *O*-dimethylcitromycin (Found : C, 52·9; H, 4·0; N, 12·1; OMe, 12·7%). The orange zone was washed through the column with a chloroform–methanol mixture (9 : 1), and on crystallisation from chloroform and then from ethyl acetate gave the 2 : 4-dinitrophenylhydrazone of 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin (1 g.) in small orange tablets, m. p. 220° (decomp.) [Found : C, 51·6; H, 3·9; N, 12·4; OMe, 14·6. $C_{17}H_{10}O_7N_4(OMe)_2$ requires C, 51·3; H, 3·6; N, 12·6; OMe, 14·0%]. A synthetical specimen of this hydrazone was obtained as follows. The crude reaction product (0·3 g.) from the condensation of 2-hydroxy-4 : 5-dimethoxybenzoylacetone (1 g.) and ethyl carbonate (10 ml.), carried out according to the procedure described in Part II (*loc. cit.*), was dissolved in alcohol and treated with excess of alcoholic 2 : 4-dinitrophenylhydrazine sulphate. Next day the precipitate was collected, dried, dissolved in chloroform, and chromatographed on aluminium oxide, giving (1) a small zone washed through the column with chloroform, (2) an orange-yellow zone washed through with chloroform–methanol (9 : 1), and (3) a large dirty zone eluted with methanol. The residue left on the evaporation of the chloroform–methanol eluate containing zone (2) was crystallised from ethyl acetate, giving the 2 : 4-dinitrophenylhydrazone of 4-hydroxy-6 : 7-dimethoxy-3-acetylcoumarin in orange prisms, m. p. 220° (decomp.), identical with a specimen from natural sources (Found : C, 51·7; H, 3·7; N, 12·8; OMe, 14·9%).

The 2 : 4-dinitrophenylhydrazone of acetone could not be detected.

(*b*) Prepared according to method (*a*), the hydrolysate was extracted with ether (4 × 100 ml.) and the extract dried and evaporated, leaving a crystalline residue which on recrystallisation from ethyl acetate and then from methyl alcohol gave 4-*hydroxy*-6 : 7-*dimethoxy*-3-*acetylcoumarin* in colourless needles (0·2—0·3 g.), m. p. 208°, readily soluble in aqueous sodium hydroxide or sodium carbonate, more slowly soluble in sodium hydrogen carbonate, and giving a faint pale brown ferric reaction in alcohol which gradually darkened when the solution was warmed (Found : C, 59·3; H, 5·0; *M*, 241·2. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%; *M*, 264). This compound gave the 2 : 4-dinitrophenylhydrazone, forming orange tablets, m. p. 220° (decomp.), from ethyl acetate, identical with the product obtained by method (*a*).

Continuous extraction of the aqueous liquors with ether in an extractor gave only a further small amount of the acetylcoumarin, together with unchanged *O*-dimethylcitromycinone (0·6 g.).

Degradation of 4-*Hydroxy*-6 : 7-*dimethoxy*-3-*acetylcoumarin with Alkali.*—A solution of the compound

(0·5 g.) in 2N-sodium hydroxide (25 ml.) was heated on the steam-bath for ½ hour, cooled, acidified with 2N-sulphuric acid, kept for 24 hours, filtered to remove a trace of solid, and treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate. From a benzene extract of the resulting precipitate (0·1 g.), the 2 : 4-dinitrophenylhydrazones of acetone, m. p. 125°, and of 2-hydroxy-4 : 5-dimethoxyacetophenone, m. p. 228°, were isolated by liquid chromatography with benzene as the solvent on a column of aluminium oxide, and identified by comparison with authentic specimens. Distillation of the aqueous liquor left on the separation of the crude hydrazones gave acetic acid which was identified by conversion into the anilide, m. p. and mixed m. p. 112°.

The residue, insoluble in benzene, was 4-hydroxy-6 : 7-dimethoxycoumarin, which separated from ethyl acetate in colourless prisms, m. p. 278°, identical with an authentic specimen (*loc. cit.*).

The degradation of the 3-acetylcoumarin was repeated, and the acidified liquors extracted with chloroform (3 × 25 ml.). From the chloroform extracts, 2-hydroxy-4 : 5-dimethoxybenzoic acid was isolated with the aid of aqueous sodium hydrogen carbonate and purified from aqueous acetone, forming colourless needles, m. p. 214°, identical with an authentic specimen.

Hydration of O-*Dimethylcitromycinone.*—A mixture of the dimethyl ether (0·5 g.), dioxan (50 ml.), water (5 ml.), palladium–charcoal (0·3 g., containing 10% of palladium), and 2N-hydrochloric acid (1 ml.) was boiled under reflux for 10 minutes, filtered (wash charcoal with dioxan), and the solvent evaporated under reduced pressure. Crystallisation of the residue from alcohol or aqueous alcohol gave the hydration *product* in very pale green needles (0·4 g.), m. p. 201°, having a reddish brown ferric reaction in alcohol [Found : C, 58·8; H, 4·6; OMe, 19·9. $C_{13}H_8O_5(OMe)_2$ requires C, 58·8; H, 4·6; OMe, 20·3%]. This compound dissolves very slowly in aqueous sodium hydrogen carbonate, but is readily soluble in aqueous sodium hydroxide. In attempts to hydrogenate dimethylcitromycinone (0·5 g.) dissolved in dioxan (60 ml.) with hydrogen and palladium–charcoal catalyst (from 0·5 g. of charcoal and 0·2 g. of palladium chloride), the same compound (0·4 g.), m. p. 201° after purification, was obtained. A mixture of this substance (0·25 g.), hydroxylamine hydrochloride (0·1 g.), sodium acetate (0·1 g.), and alcohol (25 ml.) was heated on the steam-bath for 6 hours; on cooling, the oxime of *O*-dimethylcitromycinone was deposited in pale greenish needles, m. p. 268° (decomp.), identical with an authentic specimen (Found : C, 59·6; H, 4·3. $C_{15}H_{13}O_5N$ requires C, 59·4; H, 4·3%). On being heated with aniline (0·2 g.) in acetic acid (2 ml.) at 100° for 5 minutes the hydration product gave rise to the anil of *O*-dimethylcitromycinone, m. p. 252°, identical with an authentic specimen, after purification from dioxan or acetic acid.

Attempts to acetylate the hydration product by the acetic anhydride–pyridine or the sodium acetate method regenerated *O*-dimethylcitromycinone, m. p. 316° (decomp.). Dimethylcitromycinone, m. p. 316° (decomp.), was almost quantitatively regenerated when the substance (0·1 g.) was dissolved in concentrated sulphuric acid (3 ml.), and the solution diluted immediately with water.

A solution of the hydration product (0·5 g.) in 2N-sodium hydroxide (20 ml.) was heated on the steam-bath for 10 minutes, diluted with water (25 ml.), acidified with sulphuric acid, filtered to remove a trace of solid, and treated with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate. Next day the solid (0·3 g.) was isolated, dried, and extracted with benzene, leaving an insoluble residue (0·1 g.) which, on crystallisation from ethyl acetate, gave 4-hydroxy-6 : 7-dimethoxycoumarin, m. p. and mixed m. p. 278° (decomp.), identical with a synthetical specimen. From the benzene extracts of the crude coumarin the 2 : 4-dinitrophenylhydrazones of acetone, m. p. 125°, and of 2-hydroxy-4 : 5-dimethoxyacetophenone, m. p. 228°, were isolated by chromatography on aluminium oxide and identified by comparison with authentic specimens.

A slow stream of ozone and oxygen was passed for 45 minutes into a solution of the hydrate (1 g.) in chloroform (75 ml.) kept at 0°, and, after the evaporation of the solvent, the residue was treated with water (100 ml.). Next day the almost clear solution was mixed with excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate, and the product (0·6 g.) dissolved in chloroform and separated into 4 fractions by means of liquid chromatography on aluminium oxide. Of these, the main fraction consisted of the 2 : 4-dinitrophenylhydrazone, forming orange needles, m. p. 236°, identical with material obtained from alkaline hydrolysis of dimethylcitromycinone. Two of the remaining fractions consisted of small amounts of resinous materials, whilst the remaining fraction, forming red needles, m. p. above 300°, from methanol, was too small for investigation. Distillation of the filtrate from the mixed solid gave acetic acid which was identified by conversion into the anilide, m. p. and mixed m. p. 112°.

Oxidation of Methyl O-*Dimethylcitromycetin* (*with* J. B. D. MacKenzie).—A solution of potassium permanganate (4 g.) in water (75 ml.) was gradually added to the ester (1 g.) dissolved in acetone (100 ml.) during 6 hours. Next day the mixture was clarified with sulphur dioxide, the greater part of the acetone was removed under reduced pressure, the residue was extracted with ether (6 × 100 ml.), and the combined dried extracts were evaporated. Crystallisation of the residual solid from methanol gave *2-hydroxy-6-carbomethoxy-4 : 5-dimethoxybenzoic acid* in colourless plates (0·2 g.), m. p. 145°, having a purple ferric reaction in alcohol [Found : C, 51·6; H, 4·8; OMe, 34·8. $C_8H_3O_4(OMe)_3$ requires C, 51·6; H, 4·7; OMe, 36·3%]. In some oxidation experiments only a trace of this acid was obtained, and another substance was encountered which formed colourless needles, m. p. 267—268° (decomp.), from methanol, and had a negative ferric reaction (Found : C, 61·7; H, 6·12; OMe, 30·5%). The half-ester of the phthalic acid (0·075 g.), dissolved in ether (20 ml.), was treated with excess of diazoethane (from 0·3 g. nitrosoethylurea) in ether (20 ml.), and next day the solvent was evaporated and the residue crystallised from light petroleum (b. p. 60—80°), giving the methyl ethyl ester of 5 : 6-dimethoxy-3-ethoxyphthalic acid (0·05 g.), m. p. 96—97°. To a solution of this compound (0·05 g.) in methanol (5 ml.), 4% methanolic potassium hydroxide (2 ml.) was added followed by water (2 ml.), and the mixture was boiled under reflux for ½ hour, cooled, neutralised (Congo-red) with dilute hydrochloric acid, and evaporated under reduced pressure. By means of ethyl acetate, 5 : 6-dimethoxy-3-ethoxyphthalic acid was isolated from the residue, and on crystallisation from ethyl acetate–light petroleum formed slender prisms (0·03 g.), m. p. 195° (with effervescence), identical with a synthetical specimen (Part I, this vol., p. 497). By being sublimed in a vacuum at 190°/14 mm., this acid was converted into the anhydride which on recrystallisation from ethyl acetate–light petroleum had m. p. 196°, undepressed on

admixture with a synthetical specimen (Part I, *loc. cit.*) (Found : C, 57·5; H, 5·0. Calc. for $C_{13}H_{12}O_4$: C, 57·2; H, 4·8%).

Very considerable difficulties have been encountered in obtaining consistent analytical results from the same samples of *O*-dimethylcitromycinone, *O*-dimethylcitromycinol, and their derivatives.

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UNIVERSITY OF LIVERPOOL. [*Received, May 18th,* 1948.]

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183. *The Chemistry of Fungi. Part IV. The Constitution of the Phenol,* $C_{11}H_{16}O_3$, *from Citrinin.*

By J. P. BROWN, N. J. CARTWRIGHT, ALEXANDER ROBERTSON, and W. B. WHALLEY.

The isomeric phenols (A) and (B), $C_{11}H_{16}O_3$, obtained by the hydrolytic fission of citrinin with dilute alkalis as well as with dilute acids, form liquid dimethyl ethers which are readily characterised by the formation of *p*-nitrobenzoates and hydrogen phthalates. On resolution with the aid of strychnine or brucine the hydrogen phthalate of the dimethyl ether of (B) is separated into (+)- and (−)-forms, of which the latter is identical with the hydrogen phthalate derived from the dimethyl ether of (A). The phenol, $C_9H_{12}O_2$, formed by the fusion of (A) with alkalis is identical with synthetical 4-methyl-5-ethylresorcinol. Like the latter compound phenols (A) and (B) readily give bisphenylazo-derivatives. Reduction of (A) or (B) with hydriodic acid and red phosphorus yielded the phenol (XIV; R = Me), the structure of which was determined by two independent syntheses. Finally a synthesis of the *p*-nitrobenzoate of the dimethyl ether of (B) has been achieved, and thus the constitution of phenols (A) and (B) has been established.

THE lævo-rotatory, yellow, phenolic carboxylic acid, citrinin, $C_{13}H_{14}O_5$, a characteristic metabolic product of several strains of *Penicillium citrinum* grown on a Czapek–Dox glucose medium, and also produced by *Aspergillus* species, *A. terreus* and the *candidus* group, was first isolated by Hetherington and Raistrick (*Phil. Trans.*, 1931, *B*, **220**, 269) who, *inter alia*, described the general properties of this interesting compound and showed that on being boiled with dilute sulphuric acid it was decomposed :

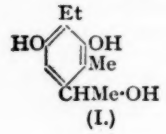
$$C_{13}H_{14}O_5 \xrightarrow{2H_2O} C_{11}H_{16}O_3 + H{\cdot}CO_2H + CO_2.$$

The substance $C_{11}H_{16}O_3$ was found to be a mixture of two isomerides, one of which was optically active (lævo-rotatory), and was referred to as " product A," whilst the second substance was optically inactive, and was named " product B; " the designations (A) and (B) have been retained for the present. Further, these authors concluded that (A) and (B) were dihydric phenols in which the third oxygen atom was present as an alcoholic-hydroxyl group, and they showed that on fusion with potassium hydroxide product (A) gave rise to a dihydric phenol, $C_9H_{12}O_2$, forming a dimethyl ether, $C_9H_{10}(OMe)_2$, which on oxidation with alkaline potassium permanganate yielded two acidic products, $C_{10}H_{12}O_4$ and $C_{11}H_{14}O_4$. From an examination of the phenol and of the oxidation products of its methyl ether, Coyne *et al.* (*Phil. Trans.*, 1931, *B*, **220**, 301) concluded that the compound was 4-methyl-2-ethylresorcinol and on this basis developed structural formulæ for (A) (I), and for citrinin. Subsequently Robinson and Shah (*J.*, 1934, 1491) synthesised 4-methyl-2-ethylresorcinol, but were unable to equate this compound with the phenolic degradation product from (A) (cf. Sprenger and Ruoff, *J. Org. Chem.*, 1946, **11**, 189). Of interest in this connexion are the results of Gore *et al.* (*Nature*, 1946, **157**, 333) who state that citrinin reacts with diazonium salts in the normal way to give monoazo-derivatives, and that this coupling is not accompanied by the displacement of any groups during the condensation. Further, the Indian authors found that, whilst (A) couples normally with the diazonium salt from 5-nitro-*o*-anisidine to give a bisazo-compound, with an excess of the salt from aniline the phenol behaves abnormally. On the basis of the foregoing results it appeared that phenol (A) and citrinin did not have the structures originally assigned to them.

Since citrinin has been shown to possess considerable antibiotic activity against Gram-positive organisms (Raistrick and Smith, *Chem. and Ind.*, 1941, **60**, 828; Oxford, *ibid.*, 1942, **61**, 48) an examination of its constitution was undertaken as part of a comprehensive investigation on chemical constitution and antibiotic activity. For the development of a rational structure for citrinin the determination of the orientation of the products (A) and (B) appeared to be an essential preliminary step, and accordingly the present communication deals with this topic. The compound (A) has now been obtained by the action of boiling dilute sodium hydroxide on

citrinin, and under these conditions does not seem to be accompanied by appreciable amounts of phenol (B) which, however, can be obtained from (A) by the action of warm dilute sulphuric acid. The liquid dimethyl ether of (A), which can be prepared readily by the methyl iodide–potassium carbonate method, is conveniently characterised by the formation of a (−)-p-*nitrobenzoate* and a (−)-*hydrogen phthalate*. Similarly the liquid dimethyl ether of (B) affords an optically inactive p-*nitrobenzoate* and a *hydrogen phthalate*. Further, (A) and (B) react with warm alcoholic diazoaminobenzene, yielding isomeric *bisphenylazo*-derivatives, the compositions of which clearly indicate that the condensation is not preceded by the extrusion of an alkyl group, thus clearly establishing that there are not more than two side chains in (A) or (B). This result is supported by the fact that on oxidation with aqueous potassium permanganate the dimethyl ether of (A) gives rise to 3 : 5-dimethoxyphthalic acid (VIII).

In order to establish that (B) is the (±)-form of (A) as suggested by Hetherington and Raistrick (*loc. cit.*), and not a structural isomeride, the resolution of the optically inactive hydrogen phthalate of the dimethyl ether of (B) was undertaken. With (−)-strychnine and (−)-brucine, this derivative yields stable salts, and the (−)-*strychnine* and the (−)-*brucine* (+)-"*base*" *phthalate* separated from the acetone reaction mixtures in an almost pure state, whilst in both cases the comparatively pure salts of (−)-base (−)-acid remained in solution. Decomposition of the latter derivatives gave in each case the same (−)-hydrogen phthalate, identical in every way with the hydrogen phthalate of the dimethyl ether of phenol (A). Further, the decomposition of each of the " crossed salts " gave the same (+)-*hydrogen phthalate* of the dimethyl ether of (+)-(B), and a mixture of this ester with an equal amount of the (−)-isomeride gave rise, on recrystallisation, to an optically inactive hydrogen phthalate identical with the derivative prepared from the dimethyl ether of (B). Consequently it is clear that (A) and (B) are stereoisomerides and not structural isomerides.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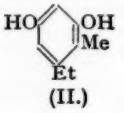
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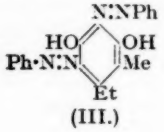
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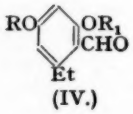
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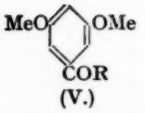
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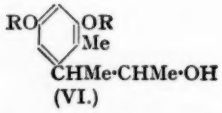
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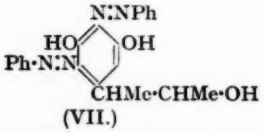
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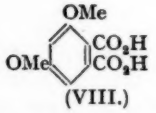
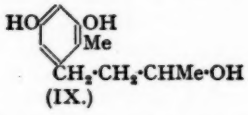
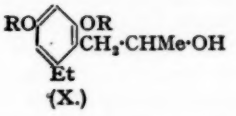
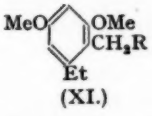

(VIII.)

The phenol, $C_9H_{12}O_2$, which is formed along with acetic acid by the fusion of (A) or (B) with potassium hydroxide appears to exist in hydrated and anhydrous forms, but is more conveniently characterised by the formation of a *di*-p-*nitrobenzoate*, and by conversion into the corresponding *aldehyde* according to Gattermann's procedure, a reaction which, in conjunction with the red-brown alcoholic ferric reaction of the product, clearly confirms the view that this phenol and therefore product (A) belong to the resorcinol series. Further, as would be expected from the behaviour of (A) the phenol, $C_9H_{12}O_2$, reacts readily with warm alcoholic diazoaminobenzene, forming a *bisphenylazo-derivative*. In order to establish the orientation of the phenol, $C_9H_{12}O_2$, the isomeric alkyl-resorcinols of the methyl-ethyl, *n*-propyl, and *iso*propyl series were synthesised, and it was ultimately found that the compound was identical with synthetical 4-methyl-5-ethylresorcinol (II) which was obtained by application of the Clemmensen reaction to 2 : 4-*dihydroxy*-6-*ethylbenzaldehyde* (IV; R = R_1 = H) prepared from 5-ethylresorcinol (the synthesis of the remaining alkyl-resorcinols will be described in a subsequent communication). Consequently the bisphenylazo-derivative of (II) must have formula (III). In preference to the route employed by Asahina and Ihara (*J. Pharm. Soc. Japan*, **1928**, **48**, 28) the ketone (V; R = Me), required for the preparation of 5-ethylresorcinol, was synthesised from 3 : 5-dimethoxybenzoic acid by way of the acid chloride (V; R = Cl) and the diazoketone (V; R = CHN_2). The reduction of the ketone (V; R = Me) with amalgamated zinc and boiling hydrochloric acid under the usual conditions gave mainly an intractable gum (compare Asahina and Ihara, *loc. cit.*, of whose work we have been able to consult only an abstract), but the use of benzene in the reduction mixture gave a satisfactory yield of 5-ethylresorcinol. The latter phenol was also obtained in good yield when the semicarbazone of the ketone was subjected to the Wolff–Kishner method of reduction. The orientation of the aldehyde (IV; R = R_1 = H) from 5-ethylresorcinol is established by the fact that two isomeric monomethyl ethers (IV; R = Me,

R_1 = H) and (IV; R = H, R_1 = Me) have been obtained from it. Of these one must be *2-hydroxy-4-methoxy-6-ethylbenzaldehyde* (IV; R = Me, R_1 = H) since it gives an intense alcoholic ferric reaction, and readily condenses with acetophenone under standard conditions to give *7-methoxy-5-ethylflavylium chloride*. The second *ether*, which does not give a ferric reaction or form a pyrylium salt, must have the orientation (IV; R = H, R_1 = Me). Although in spite of repeated efforts we were unable to effect a stepwise degradation of the dimethyl ether of (A) with oxidising agents, *e.g.*, potassium permanganate, chromic oxide, or the Oppenauer–Pondorff reaction, it seemed reasonably certain that, in view of the ready formation of acyl derivatives of the dimethyl ether of (A) and its resistance to dehydration (*e.g.* by hot Grignard reagents), the alcoholic-hydroxyl group in (A) was not tertiary. On this account and because (A) gives a bisphenylazo-derivative and can be degraded to 4-methyl-5-ethylresorcinol (II) by the loss of the group CHMe·OH as acetic acid it seemed probable that (A) was a secondary alcohol for which there are three possible formulæ (VI; R = H), (IX), and (X; R = H). Of these structures (VI; R = H) or (X; R = H) appeared to be the more likely.

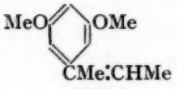

(IX.)


(X.)


(XI.)

Accordingly syntheses of the methyl ethers (VI; R = Me) and (X; R = Me) were undertaken. In the preparation of the latter compound the *aldehyde* (IV; R = R_1 = Me) was converted into the *azlactone* by the standard method, and on hydrolysis this compound gave the phenylpyruvic acid (XI; R = CO·CO_2H), the *oxime* of which [XI; R = C(:NOH)·CO_2H] was converted into the *cyanide* (XI; R = CN). Reduction of the latter by the stannous chloride method gave a moderate yield of 2 : 4-*dimethoxy-6-ethylphenylacetaldehyde* (XI; R = CHO), and on treatment with methylmagnesium iodide this aldehyde gave the alcohol (X; R = Me) which was isolated as the p-*nitrobenzoate*, isomeric and not identical with the corresponding derivative of (B).

Before attempting the synthesis of the compounds having the remaining possible structures for the dimethyl ether of (B) it was decided to reduce the alcoholic-hydroxyl groups of (A) or (B), and then by synthesis to define the exact nature of the two alkyl groups in the product. By reduction of (A) or (B) with hydriodic acid and red phosphorus a dihydric *phenol*, containing all the carbon atoms present in (A), was obtained which was readily characterised by the formation of a *di*-p-*nitrobenzoate*, and was oriented by two independent syntheses.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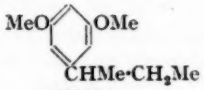
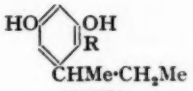
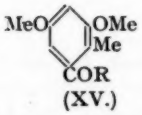
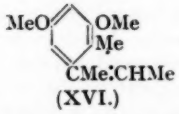
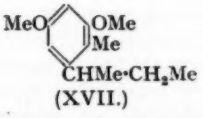

(XIII.)


(XIV.)


(XV.)


(XVI.)

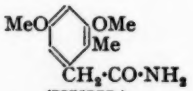

(XVII.)

In the first synthesis interaction of 3 : 5-dimethoxyacetophenone (V; R = Me) with excess of warm ethylmagnesium iodide and simultaneous dehydration of the initial product yielded the *phenylbutene* (XII), and on hydrogenation this compound furnished the *phenylbutane* (XIII) which was demethylated giving 2-(3 : 5-*dihydroxyphenyl*)*butane* (XIV; R = H). Prepared from (XIV; R = H) by Gattermann's method, the *aldehyde* (XIV; R = CHO) was reduced by Clemmensen's method, giving 2-(3 : 5-*dihydroxy-2-methylphenyl*)*butane* (XIV; R = Me), identical in every way with the phenol obtained from (A) or (B). In the second procedure the *acid* (XV; R = OH), prepared by the methylation of 3 : 5-dihydroxy-2-methylbenzoic acid, was converted into the diazoketone (XV; R = CHN_2) by way of the acid chloride (XV; R = Cl) and on treatment with hydriodic acid the diazene gave rise to the *ketone* (XV; R = Me), the interaction of which with ethylmagnesium iodide furnished the phenylbutene (XVI). 2-(3 : 5-*Dimethoxy-2-methylphenyl*)*butane* (XVII) was then prepared by the hydrogenation of the butene, and on demethylation gave the phenol (XIV; R = Me) shown to be identical with the natural compound by comparison of the di-*p*-nitrobenzoates.

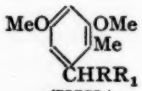
Having thus established the carbon skeleton of the substituent groups of (A) and (B) it

seemed to us reasonably certain that these compounds had the constitution (VI; R = H) and accordingly a synthesis of the *p*-nitrobenzoate of the dimethyl ether of (B) was carried out as follows.

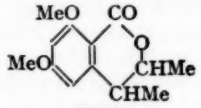
On being subjected to the Wolff rearrangement with ammoniacal silver nitrate the diazoketone (XV; R = CHN_2) furnished an excellent yield of the *amide* (XVIII) which was converted into 3 : 5-*dimethoxy-2-methylbenzyl cyanide* (XIX; R = H, R_1 = CN) by dehydration. The



(XVIII.)



(XIX.)



(XX.)

carbon methylation of this cyanide by the interaction of the sodio-derivative with methyl sulphate in benzene appeared to give a mixed product but, owing to the lack of material, it was distilled and used directly in the next stage. Reduction of this distillate by the stannous chloride method furnished aldehydic material, and on condensation with methylmagnesium iodide the latter yielded an alcoholic product which in the crude state was acylated with *p*-nitrobenzoyl chloride–pyridine mixture. Fractional crystallisation of the resulting mixed ester gave a small yield of a *p*-nitrobenzoate, identical in every respect with the *p*-nitrobenzoate of the dimethyl ether of (B). Along with this derivative there was isolated in larger amount a second p-*nitrobenzoate* which from its analytical results appeared to be derived from an alcohol containing a methylene residue more than the dimethyl ether of (B), *i.e.* arising in the synthesis owing to the required intermediate cyanide (XIX; R = Me, R_1 = CN) being contaminated with the $\alpha\alpha$-dimethyl homologue, with the result that the aldehyde (XIX; R = Me, R_1 = CHO) contained the corresponding higher homologue. In spite of the fact that we have not been able at present to define the intermediate stages in this synthesis it is clear that the production of a mixture containing the *p*-nitrobenzoate of the dimethyl ether of (B) from the cyanide (XIX; R = H, R_1 = CN) by the procedure employed, in conjunction with the conversion of (B) into (XIV; R = Me), affords conclusive proof that (B) and consequently (A) have the constitution (VI; R = H). Further, the bisphenylazo-derivative of (A) is represented by formula (VII), and the lactone, $C_{11}H_{10}O_2(OMe)_2$, formed by the oxidation of the dimethyl ether of (A) (Hetherington and Raistrick, *loc. cit.*) is represented by (XX). In connexion with the constitution (VI, R = H) assigned to (A) it may be noted that an alcohol of this structure, having two asymmetric carbon atoms, may exist in four optical isomerides, forming two pairs of (±)-forms capable of being separated by crystallisation. Since a derivative of (B) has been resolved to give the corresponding derivative of (A) it would seem that (B) is probably one of two possible (±)-forms and not a mixture of all four isomerides, but the elucidation of this problem must await the results of further synthetical investigations on the stereochemistry of (VI; R = H), which are in progress.

The starting material (XV; R = OH) employed in the synthesis of the dimethyl ether of (B) was obtained from 3 : 5-dihydroxy-2-methylbenzoic acid, but we have encountered considerable difficulty in preparing this acid. As far as we are aware the only recorded preparation of the compound is that of Jacobsen and Wierss (*Ber.*, 1883, **16**, 1960) involving the sulphonation of *o*-toluic acid, and subsequent fusion of the resulting disulphonic acid with potassium hydroxide, for which insufficient details have been recorded (cf. Liebermann and Kostanecki, *Annalen*, 1887, **240**, 280). The application of the Clemmensen method of reduction to 3 : 5-dihydroxy-2-formylbenzoate as an alternative route to 3 : 5-dihydroxy-2-methylbenzoic acid gave only small yields of the required product accompanied by much resinous material. Consequently, in order to obtain a satisfactory source of 3 : 5-dihydroxy-2-methylbenzoic acid we are re-investigating its preparation from *o*-toluic acid.

After the completion of the work on the orientation of phenol (A) our attention was directed to an editorial communication by Cram (*J. Amer. Chem. Soc.*, 1948, **70**, 440) announcing the synthesis of 4-methyl-5-ethylresorcinol without giving experimental details (compare *Nature*, 1948, **162**, 72).

Experimental.

Derivatives of Phenols (A) *and* (B).—A solution of citrinin (1 g.) in 10% aqueous sodium hydroxide (50 ml.) was heated under reflux for 3½ hours in an atmosphere of nitrogen, and the cooled mixture saturated with carbon dioxide, and extracted several times with ether. Evaporation of the dried ethereal extracts gave the phenol (A) (0·5 g.), m. p. 128°, after recrystallisation from chloroform and subsequent de-solvation.

When boiling solutions of phenol (A) (0·5 g.) in alcohol (15 ml.) and diazoaminobenzene (2 g.) in alcohol (15 ml.) were mixed and kept at room temperature for several days the red *bisphenylazo*-derivative of (A) separated. Recrystallised from alcohol, the compound formed deep-red glistening needles, m. p. 204—205° (Found: C, 68·2; H, 6·0; N, 14·0. $C_{32}H_{24}O_2N_4$ requires C, 68·3; H, 5·9; N, 13·8%). When (B) was subjected to the same reaction a *bisazo*-derivative was obtained which separated from alcohol in deep-red needles, m. p. 222—223° (Found: N, 13·8%). A mixture of the two azo-derivatives from (A) and (B) melted at 204—206°, and after recrystallisation from alcohol at 204—207°.

The phenol (A) (5 g.) was methylated with excess of methyl iodide and potassium carbonate in boiling acetone during 16—20 hours, until a sample was completely insoluble in dilute aqueous sodium hydroxide. An ethereal solution of the product was washed with aqueous sodium hydroxide and then with water, dried, and evaporated, leaving an almost quantitative yield of the dimethyl ether of (A) which on distillation in a vacuum was obtained as a colourless oil, b.p. 146—148°/0·5 mm., and was characterised by the formation of a p-*nitrobenzoate* by the *p*-nitrobenzoyl chloride–pyridine method, forming characteristic yellow rhombic prisms, m. p. 92—93°, from alcohol; $[\alpha]_D^{18°}$ −22·5° (*c*, 5·0 in chloroform [Found: C, 64·2; H, 5·9; N, 3·4; OMe, 17·0. $C_{18}H_{17}O_4N(OMe)_2$ requires C, 64·3; H, 6·2; N, 3·8; OMe, 16·6%].

Similarly, the phenol (B) was methylated and converted into the p-*nitrobenzoate* of the dimethyl ether which separated from alcohol in pale yellow lozenge-shaped prisms, m. p. 108—109° (Found: C, 64·2; H, 6·1; N, 3·7; OMe, 16·1%). A mixture of the dimethyl ether of (B) (2·8 g.), phthalic anhydride (2·0 g.), and pyridine (15 ml. was kept at 100° for 3 hours, the cooled solution was poured into dilute hydrochloric acid, and the *hydrogen phthalate*, which gradually solidified on being triturated with water, was crystallised from chloroform, forming colourless prisms (4 g.), m. p. 144° [Found: C, 67·5; H, 6·4; *M* (by titration), 376. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%; *M*, 372].

A suspension of the dimethyl ether of (A) in boiling water (1500 ml.) was vigorously agitated, and was treated with powdered potassium permanganate (40 g.) added gradually in portions of 1 g. during 1½ hours, the hot solution was filtered to remove manganese dioxide, and the filtrate evaporated under diminished pressure. On being kept, a solution of the residue in dilute hydrochloric acid slowly deposited 3 : 5-dimethoxyphthalic acid, m. p. 158° after recrystallisation from hot water, which gave the anhydride, m. p. 149°. This acid and its anhydride were identified by comparison with authentic specimens prepared according to Oxford and Raistrick's method (*Biochem. J.*, 1932, **26**, 1902).

Resolution of the Hydrogen Phthalate of the Dimethyl Ether of (B).—The phthalate (7 g.), dissolved in acetone (50 ml.), was added to a solution of strychnine (6·6 g.) in boiling acetone (1500 ml.), and 18 hours later the mixture was concentrated giving three crops of crystalline material which had almost identical melting points and specific rotations. The combined products (6·0 g.) were fractionally crystallised from alcohol, but each fraction of the *strychnine* salt was found to be identical, forming pearly plates, m. p. 213—214°, $[\alpha]_D^{18°}$ −26·5° (*c*, 4·07 in chloroform) (Found: C, 71·1; H, 6·5; N, 4·1. $C_{21}H_{24}O_6,C_{21}H_{22}O_2N_2$ requires C, 71·4; H, 6·5; N, 4·0%). A solution of this salt in the minimum amount of acetone was added to water (100 ml.) and concentrated hydrochloric acid (20 ml.), and on being kept the oil thus precipitated slowly solidified. Recrystallised from chloroform–light petroleum, the (+)-*hydrogen phthalate* of the dimethyl ether of (+)- (B) formed dense, colourless prisms, m. p. 112—114°, $[\alpha]_D^{18°}$ +31·0° (*c*, 5·0 in chloroform) (Found: C, 67·7; H, 6·4. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%).

On evaporation, the acetone liquors left after the separation of the crystalline strychnine salt gave a solid which could not be satisfactorily recrystallised, but which on treatment with acetone containing dilute hydrochloric acid gave the (−)-*hydrogen phthalate* of the dimethyl ether of (−)- (B) which formed colourless prisms, m. p. 112—114°, $[\alpha]_D^{18°}$ −30·0° (*c*, 5·0 in chloroform), from chloroform–light petroleum (b. p. 80—100°); yield almost theoretical (Found: C, 67·5; H, 6·4. $C_{21}H_{24}O_6$ requires C, 67·7; H, 6·5%). This isomeride was identical in every way with a specimen of the hydrogen phthalate, m. p. 112—114°, $[\alpha]_D^{18°}$ −30·0°, prepared directly from the dimethyl ether of (A). A mixture composed of equal weights of the (+)- and (−)-hydrogen phthalates was recrystallised from chloroform–light petroleum, and was obtained in colourless prisms, m. p. 144°, undepressed on admixture with an authentic specimen prepared from the dimethyl ether of inactive (B).

A mixture of the hydrogen phthalate of the dimethyl ether of (B) (7 g.) and brucine (7·0 g.) was dissolved in boiling acetone (150 ml.), and on being concentrated and cooled the mixture deposited the (−)-*brucine* salt (6·0 g.), m. p. 169—171°, which could not be further resolved by fractional crystallisation. This substance separated from acetone in tiny needles, m. p. 171°, $[\alpha]_D^{18°}$ −25·6° (*c*, 4·07 in chloroform) (Found: C, 68·6; H, 6·7; N, 4·0. $C_{21}H_{24}O_6,C_{23}H_{26}O_4N_2$ requires C, 68·9; H, 6·6; N, 3·7%). Decomposition of this salt with dilute hydrochloric acid–acetone gave the (+)-hydrogen phthalate, m. p. 112—114°, $[\alpha]_D^{18°}$ +32° (*c*, 5·0 in chloroform) after purification. Evaporation of the acetone liquor, left after the separation of the (−)-brucine salt, gave the isomeric salt of the (−)-base (+)-acid, which on decomposition yielded the (−)-hydrogen phthalate, m. p. 112—114°, $[\alpha]_D^{18°}$ −29·4° (*c*, 5·0 in chloroform), after having been recrystallised from chloroform–light petroleum (b. p. 80—100°).

2 : 4-*Dimethoxy*-6-*ethylbenzaldehyde* (IV; R = R_1 = H).—3 : 5-Dimethoxybenzoyl chloride (9 g., prepared by the interaction of molecular proportions of the acid and phosphorus pentachloride), dissolved in ether (100 ml.), was slowly added to a well-agitated solution of diazomethane (from 25 g. of nitrosomethylurea), and after the vigorous evolution of nitrogen had subsided the mixture was kept for 1 hour, and the ether and excess of diazomethane removed by distillation. A solution of the residual crystalline diazoketone in chloroform (200 ml.) was vigorously agitated with hydriodic acid (30 ml.; *d* 1·7) for 10 minutes and, after the addition of water, the chloroform layer was separated, washed successively with aqueous sodium thiosulphate, aqueous sodium hydroxide, and water, and dried, and evaporated, leaving 3 : 5-dimethoxyacetophenone (V; R = Me) as a colourless oil (7·5 g.), b. p. 122°/0·5 mm., which gave a theoretical yield of the semicarbazone, m. p. 190° (Found: C, 55·4; H, 6·2. Calc. for $C_{11}H_{15}O_3N_3$: C, 55·7; H, 6·4%) (compare Asahina and Ihara, *loc. cit.*, who gave m. p. 187° for the semicarbazone). The ketone readily gave a 2 : 4-*dinitrophenylhydrazone*, forming orange prisms or red needles, m. p. 191°, from acetic acid (Found: C, 53·3; H, 4·5; N, 15·1. $C_{16}H_{16}O_6N_4$ requires C, 53·3; H, 4·5; N, 15·6%). The hydrazone of this ketone appeared to be a liquid, but when insufficient hydrazine

hydrate was employed in its preparation the *ketazine* was obtained, forming yellow prisms, m. p. 127·5°, from methanol (Found: C, 67·5; H, 7·0; N, 7·4. $C_{20}H_{24}O_4N_2$ requires C, 67·4; H, 6·8; N, 7·9%).

A mixture of the foregoing semicarbazone (7·5 g.), sodium methoxide (from 1·5 g. of sodium), and triethylene glycol (glycol bis-2-hydroxyethyl ether) (40 ml.) was kept at 200° for 1 hour, and then cooled, diluted with water (200 ml.), and extracted with ether. Evaporation of the dried extracts left 3 : 5-dimethoxyethylbenzene (4 g.), b. p. 123°/14 mm. (Asahina and Ihara, *loc. cit.*, gave b. p. 95—105°/10 mm.). The same compound was formed when 3 : 5-dimethoxyacetophenone (3·3 g.), benzene (100 ml.), concentrated hydrochloric acid (50 ml.), and amalgamated zinc (25 g.) were heated on the steam-bath for 2½ hours. After cooling, the benzene layer was separated, washed, dried, and evaporated, leaving 3 : 5-dimethoxyethylbenzene (2·1 g.), b. p. 135—140°/30 mm. Demethylation of this ether (3·5 g.) with boiling hydriodic acid (37 ml.; *d* 1·7) and acetic acid (from 25 ml. of anhydride) at 130° for 35 minutes gave an almost theoretical yield of 5-ethylresorcinol which was isolated with ether and purified by distillation in a high vacuum followed by recrystallisation from benzene, forming colourless prisms, b. p. 122°/0·1 mm., m. p. 96—97°, and giving a violet colouration with aqueous ferric chloride (compare Asahina and Ihara, *loc. cit.*, who gave m. p. 93°, and state that the phenol does not give a ferric reaction). The *di*-p-*nitrobenzoate* of this compound formed stout prisms, m. p. 175°, from acetic acid (Found: N, 6·6. $C_{22}H_{16}O_8N_2$ requires N, 6·5%). On being heated with alcoholic diazoaminobenzene 5-ethylresorcinol gave a *bisphenylazo*-derivative which separated from benzene–light petroleum (b. p. 80—100°) in small crimson prisms, m. p. 212° (decomp.) (Found: N, 16·2. $C_{20}H_{18}O_2N_4$ requires N, 16·2%).

A solution of 5-ethylresorcinol (3 g.) in ether (30 ml.), containing hydrogen cyanide (6 ml.), was saturated with hydrogen chloride at room temperature, and 18 hours later the crystalline aldimine was isolated, washed with ether, and hydrolysed with water (30 ml.) at 70—80° for ½ hour. The resulting 2 : 4-*dihydroxy*-6-*ethylbenzaldehyde* (2·5 g.) was purified by crystallisation from benzene, and then by sublimation in a high vacuum, being finally obtained in colourless prisms, m. p. 99—100° (Found: C, 64·7; H, 6·2. $C_9H_{10}O_3$ requires C, 65·1; H, 6·0%). It gave a 2 : 4-*dinitrophenylhydrazone*, separating from ethyl acetate in shining deep-crimson plates, m. p. 293° (decomp.) (Found: N, 16·5. $C_{15}H_{14}O_6N_4$ requires N, 16·2%). Prepared by the methyl iodide–potassium carbonate method, the *dimethyl ether* formed colourless prisms, m. p. 51—52°, from light petroleum (b. p. 40—60°) (Found: C, 68·0; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). The same ether was prepared directly as follows: Hydrogen chloride was led into a solution of 3 : 5-dimethoxyethylbenzene (12 g.) in ether (150 ml.), containing zinc cyanide (10 g.), for 4 hours, and 18 hours later the solid aldimine was washed by decantation with ether and hydrolysed with water (100ml.) at 80° for ½ hour. On being isolated by means of ether, and crystallised from light petroleum (b. p. 40—60°), the aldehyde (12·2 g.) was obtained in colourless prisms, m. p. 51—52°, and gave the *oxime*, forming colourless prisms, m. p. 111°, from light petroleum (b. p. 80—100°) (Found: C, 63·5; H, 7·3; N, 7·0. $C_{11}H_{15}O_3N$ requires C, 63·2; H, 7·2; N, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in long deep-red needles, m. p. 217° (decomp.) (Found: N, 14·9. $C_{17}H_{18}O_6N_4$ requires N, 15·0%).

4-*Methyl*-5-*ethylresorcinol* (II).—Prepared by the fusion of (A) or (B) with potassium hydroxide according to the directions of Hetherington and Raistrick (*loc. cit.*), who gave m. p. 97—99°, this phenol was purified by sublimation in a vacuum, and then by crystallisation from anhydrous benzene, forming stout prisms, m. p. 95—96°, which did not change on further purification by sublimation and by crystallisation (Found: C, 71·3, 70·8; H, 7·8, 7·9. Calc. for $C_9H_{12}O_2$: C, 71·1; H, 7·9%). On being recrystallised from water the phenol separated as a hydrate in needles, m. p. 66—68°, which lost part of the solvent of crystallisation on being dried in a vacuum (Found, in material dried in a vacuum at room temperature over phosphoric oxide: C, 64·9; H, 7·8. Calc. for $C_9H_{12}O_2,H_2O$: C, 63·5; H, 8·3%). On being warmed on the steam-bath with pyridine (2 ml.) and *p*-nitrobenzoyl chloride (0·6 g.) for ½ hour, the anhydrous phenol gave rise to a *di*-p-*nitrobenzoate*, forming cream prismatic plates, m. p. 203° (Found: C, 61·1; H, 4·0; N, 6·2. $C_{23}H_{18}O_8N_2$ requires C, 61·3; H, 4·0; N, 6·2%). A solution of the phenol (0·3 g.) and diazoaminobenzene (1·5 g.) in alcohol (15 ml.) was warmed on the steam-bath for 1 hour, and on cooling deposited the *bisphenylazo*-derivative in long red needles, m. p. 169—173°. Recrystallised from light petroleum (b. p. 80—100°), this compound formed reddish-orange silky needles, m. p. 178—179° (Found: C, 69·7; H, 5·3; N, 15·1. $C_{21}H_{20}O_2N_4$ requires C, 70·0; H, 5·6; N, 15·6%). Condensation of the phenol (0·5 g.) with hydrogen cyanide (1 ml.) in ether (50 ml.) was effected by means of hydrogen chloride, and 18 hours later the crystalline aldimine was hydrolysed with water (25 ml.) at 60—70° for 5 minutes. On cooling the hydrolysate deposited 4 : 6-*dihydroxy*-3-*methyl*-2-*ethylbenzaldehyde* (0·4 g.), forming colourless glistening prisms, m. p. 157—158°, from benzene and having a red-brown ferric reaction in alcohol (Found: C, 66·4; H, 7·0. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). Methylation of this compound by the methyl iodide–potassium carbonate method gave the dimethyl ether which separated from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 92°, and gave a 2 : 4-*dinitrophenylhydrazone*, forming red needles, m. p. 236°, from acetic acid (Found: C, 55·6; H, 5·6; N, 14·4. $C_{18}H_{20}O_6N_4$ requires C, 55·7; H, 5·2; N, 14·4%).

Authentic 4-methyl-5-ethylresorcinol was prepared by the reduction of 2 : 4-dihydroxy-6-ethylbenzaldehyde (IV; R = R_1 = H) (0·5 g., added in small portions during 1 hour) with a boiling mixture of concentrated hydrochloric acid (9 ml.), water (75 ml.), and alcohol (9 ml.), containing amalgamated zinc (15 g.), in the course of 3 hours, with the addition of more acid (6 ml.) and alcohol (6 ml.) after 1 hour. On isolation with ether the phenol was purified by crystallisation from benzene followed by sublimation in a vacuum, and had m. p. 95—96° and a blue ferric reaction, identical in every way with a natural specimen (Found: C, 70·8; H, 7·9%). Like the natural phenol the synthetical compound separated from water as a hydrate in needles, m. p. 66—68°, which on being dried in a vacuum desiccator at room temperature appeared to be partially dehydrated (Found: C, 64·1; H, 7·9. Calc. for $C_9H_{12}O_2,H_2O$: C, 63·5; H, 8·3%). The bisphenylazo-derivative formed long, silky red needles, m. p. and mixed m. p. 178—179°, identical with a specimen prepared from the natural phenol. Similarly the di-*p*-nitrobenzoate and the aldehyde were identical with the corresponding derivatives of the natural phenol.

Monomethyl Ethers of 2 : 4-*Dihydroxy-6-ethylbenzaldehyde.*—A mixture of the aldehyde (2 g.), methyl iodide (2 g.), potassium carbonate (4 g.), and acetone (75 ml.) was heated under reflux for 1 hour, and the filtered liquor was evaporated. A solution of the residue in ether (150 ml.) was extracted with 2N-sodium hydroxide (50 ml., 3 times), the combined extracts acidified, and the product isolated with ether and distilled in a vacuum, giving the 2-*hydroxy*-4-*methoxy*-6-*ethylbenzaldehyde* (IV; R = Me, R_1 = H) as a colourless viscous oil which gradually solidified and then formed colourless rectangular prisms, m. p. 48°, from light petroleum–ethyl acetate, having a red-brown ferric reaction in alcohol (Found : C, 66·6; H, 6·5. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright-red flat prisms, m. p. 220° (decomp.) (Found : N, 15·8. $C_{16}H_{16}O_6N_4$ requires N, 15·6%). A solution of this monomethyl ether (0·5 g.) and acetophenone (0·5 g.) in ethyl acetate was saturated with hydrogen chloride, and in the course of 48 hours 7-*methoxy*-5-*ethylflavylium chloride* separated in golden-yellow needles (0·5 g.). Crystallised from dilute hydrochloric acid, the compound formed golden-brown flat prisms decomposing at 161° (Found : Cl, 11·6. $C_{18}H_{17}O_3Cl$ requires Cl, 11·5%).

Monobenzylation of 2 : 4-dihydroxy-6-ethylbenzaldehyde (1·6 g.) was effected with benzyl bromide (1·5 ml.) and potassium carbonate (5 g.) in boiling acetone (75 ml.) during 1 hour. On isolation 2-*hydroxy*-4-*benzyloxy*-6-*ethylbenzaldehyde* (IV; R = CH_2Ph, R_1 = H) was distilled in a high vacuum, and obtained as a colourless viscous oil (2·1 g.), b. p. 165—166°/0·1 mm., giving a red-brown ferric reaction in alcohol (Found : C, 75·2; H, 6·1. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). The *oxime* of this ether formed colourless needles, m. p. 108°, from alcohol (Found : C, 70·7; H, 6·7; N, 5·3. $C_{16}H_{17}O_3N$ requires C, 70·9; H, 6·3; N, 5·2%), and the 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in shining scarlet plates, m. p. 237° (decomp.) (Found : N, 12·6. $C_{22}H_{20}O_6N_4$ requires N, 12·8%). Methylation of the monobenzyl ether with excess of methyl iodide and potassium carbonate during 12 hours gave 4-benzyloxy-2-methoxy-6-ethylbenzaldehyde (IV; R = CH_2Ph, R_1 = Me) which was purified by distillation in a high vacuum and obtained as a colourless oil (1·5 g.), b. p. 170°/0·1 mm., giving an *oxime* in colourless rectangular prisms, m. p. 133—134°, from alcohol (Found : C, 71·8; H, 6·4; N, 5·1. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 5·0%) and a 2 : 4-*dinitrophenylhydrazone*, in rosettes of scarlet needles, m. p. 179° (decomp.), from ethyl acetate (Found : N, 12·4. $C_{23}H_{22}O_6N_4$ requires N, 12·4%).

Debenzylation of the mixed ether (1·5 g.) was effected with a mixture of concentrated hydrochloric acid (10 ml.) and acetic acid (15 ml.) on the steam-bath for 10 minutes. The resulting deep-green solution was diluted with water, and on isolation with ether 4-*hydroxy*-2-*methoxy*-6-*ethylbenzaldehyde* (IV; R = H, R_1 = Me) was crystallised from benzene and then from benzene–methanol, forming colourless flat prisms, m. p. 199°, readily soluble in dilute aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 66·6; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* formed deep crimson plates, m. p. 279° (decomp.), from ethyl acetate (Found : N, 15·6. $C_{16}H_{16}O_6N_4$ requires N, 15·6%).

2-(3 : 5-*Dihydroxyphenyl*)*butane.*—Ethylmagnesium iodide (from 10 g. of magnesium) in ether (150 ml.) was added to a solution of 3 : 5-dimethoxyacetophenone (14 g.) in benzene (300 ml.), the ether was removed by distillation, the residual mixture was heated under reflux for 2 hours, the benzene was distilled off, and the residue was maintained at 100° for 2 hours, cooled, and decomposed with aqueous ammonium chloride at 0°. On isolation with ether the resulting 2-(3 : 5-*dimethoxyphenyl*)*but*-2-*ene* (XII) (12 g.) was purified by distillation in a vacuum, and obtained as a pale-yellow oil, b. p. 155°/14 mm., behaving as an unsaturated compound towards aqueous potassium permanganate and bromine water (Found : C, 75·0; H, 8·5. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). Hydrogenation of this compound with hydrogen at 74 lb./sq. in. and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) for 4 hours gave rise to a theoretical yield of 2-(3 : 5-dimethoxyphenyl)butane (XIII) as a colourless oil, b. p. 143°/13 mm. On being demethylated with boiling hydriodic acid (70 ml.; *d* 1·7) and acetic acid (from 45 ml. of anhydride) for 45 minutes this ether (10 g.) gave rise to 2-(3 : 5-dihydroxyphenyl)butane as a colourless viscous oil (7·3 g.), b. p. 143°/0·2 mm., which could not be induced to crystallise and gave a *di*-p-*nitrobenzoate*, forming slender cream prisms, m. p. 149°, from 80% acetic acid (Found : C, 61·9; H, 4·6; N, 6·3. $C_{24}H_{20}O_8N_2$ requires C, 62·1; H, 4·4; N, 6·0%).

2-(3 : 5-*Dihydroxy*-2-*methylphenyl*)*butane* (XIV; R = Me).—Interaction of the foregoing resorcinol derivative (7 g.) with zinc cyanide (8·0 g.) and excess of hydrogen chloride in ether (200 ml.) in the course of 72 hours, and subsequent hydrolysis of the oily aldimine salt with water (100 ml.) at 80° for ½ hour gave rise to 2-(3 : 5-dihydroxy-2-formylphenyl)butane (XIV; R = CHO) as an oil (7·0 g.) which was characterised by the formation of the *semicarbazone*, forming small prisms, m. p. 206°, from water (Found : C, 57·5; H, 6·7; N, 16·3. $C_{12}H_{17}O_3N_3$ requires C, 57·4; H, 6·8; N, 16·7%). Reduction of this aldehyde with a boiling mixture of concentrated hydrochloric acid (50 ml.) and alcohol (50 ml.) containing amalgamated zinc (50 g.) for 6 hours, with the addition of more acid (25 ml.) and alcohol (25 ml.) after 2 hours, furnished 2-(3 : 5-*dihydroxy*-2-*methylphenyl*)*butane* (XIV; R = Me) which was purified by distillation in a vacuum, and obtained as a viscous oil (4 g.), b. p. 135°/0·2 mm., giving a pale-blue colouration with aqueous ferric chloride and a yellow colouration with aqueous bleaching powder (Found : C, 73·6; H, 9·2. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). The *di*-p-*nitrobenzoate* separated from 90% acetic acid in glistening, slender, cream prisms, m. p. 164° (Found : C, 62·5; H, 4·8; N, 5·8. $C_{25}H_{22}O_8N_2$ requires C, 62·8; H, 4·6; N, 5·9%).

3 : 5-*Dimethoxy*-2-*methylbenzoic acid* (XV; R = OH).—*o*-Toluic acid was converted into the barium salt of the 3 : 5-disulphonic acid, and this compound was fused with potassium hydroxide according to the directions of Jacobsen and Wierss (*loc. cit.*), giving 3 : 5-dihydroxy-2-methylbenzoic acid, but the yields in the latter process were very variable, and in a considerable number of experiments the only solid acid obtained was *m*-hydroxybenzoic acid. Methylation of 3 : 5-dihydroxy-2-methylbenzoic acid with methyl sulphate and 20% aqueous sodium hydroxide followed by hydrolysis of the resulting ester gave rise to an almost quantitative yield of 3 : 5-*dimethoxy*-2-*methylbenzoic acid* which separated from benzene in well-defined, stout, rectangular prisms, m. p. 161°, readily soluble in alcohol and sparingly soluble in water (Found : C, 61·1; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). On being cooled

quickly a warm saturated solution of the acid deposited slender needles, m. p. 161°, which in contact with the solvent changed to stout rectangular prisms.

In the course of numerous experiments on the reduction of methyl 3 : 5-dihydroxy-2-formylbenzoate by Clemmensen's method, as an alternative route to 3 : 5-dimethoxy-2-methylbenzoic acid, disappointing yields of the product were invariably obtained. The following appear to be the best conditions: a solution of the formyl ester (3 g.) in methanol (60 ml.) was slowly added to a mixture of concentrated hydrochloric acid (50 ml.), water (10 ml.), and amalgamated zinc (25 g.) which was then heated under reflux for 1 hour. On isolation with ether the product, which contained only traces of acidic material, was distilled in a high vacuum, giving *methyl* 3 : 5-*dihydroxy*-2-*methylbenzoate*, b. p. 170°/0·5 mm., along with a small amount of lower-boiling oil and much resin. Crystallised from benzene–light petroleum, this ester formed thick plates, m. p. 124°; yield, 10—15% of theoretical (Found: C, 59·2; H, 5·4. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%). Methylation of this ester with methyl sulphate and aqueous sodium hydroxide and subsequent hydrolysis of the methyl ester gave rise to 3 : 5-dimethoxy-2-methylbenzoic acid, m. p. and mixed m. p. 160—161° (Found: C, 61·2; H, 6·1%). A solution of 3 : 5-dimethoxy-2-methylbenzoyl chloride (10 g., prepared by the interaction of molecular proportions of the acid and phosphorus pentachloride) in ether (200 ml.) was added during 15 minutes to an excess of ethereal diazomethane (from 28 g. of nitrosomethylurea and 200 ml. of ether) maintained at 0° for 4 hours, and then the excess of diazomethane and the solvent were removed in a vacuum, leaving the diazoketone as a mass of pale yellow needles. To a solution of this product in chloroform (150 ml.) hydriodic acid (30 ml.; *d* 1·7) was slowly added (10 minutes), with agitation of the mixture, followed by water (150 ml.) 15 minutes later. The chloroform layer was separated, washed with aqueous sodium hydrogen carbonate and aqueous sodium hydrogen sulphite, dried, and evaporated, leaving the *ketone* as an oil which was distilled in a high vacuum and then crystallised from benzene–light petroleum (b. p. 60—80°), forming colourless prisms, m. p. 40° (Found: C, 67·9; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·2%). This ketone, which reacted only slowly with carbonyl reagents, gave a 2 : 4-*dinitrophenylhydrazone* forming orange needles, m. p. 151°, from alcohol (Found: N, 15·2. $C_{17}H_{18}O_6N_4$ requires N, 15·0%). The *semicarbazone* crystallised from benzene in squat, colourless prisms, m. p. 166° (Found: N, 16·6. $C_{12}H_{17}O_3N_3$ requires N, 16·7%).

3 : 5-Dimethoxy-2-methylacetophenone (5 g.), dissolved in benzene (100 ml.), was slowly added to a well-stirred solution of ethylmagnesium iodide (from 4 g. of magnesium) in ether (125 ml.), the ether was distilled off, the benzene liquor was heated under reflux for 4 hours, the solvent was evaporated, and the residue was kept at 100° for 2 hours. Next day the product was decomposed with aqueous ammonium chloride, and the resulting 2-(3 : 5-dimethoxy-2-methylphenyl)but-2-ene (XVI) was isolated with ether and purified by distillation, being obtained as a colourless oil (5 g.), b. p. 125—135°/0·5 mm. Hydrogenation of this butene (3 g.), dissolved in alcohol (100 ml.), with a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) for 15 minutes gave rise to a quantitative yield of the *butane* (XVII) which on distillation was obtained as a colourless oil, b. p. 105°/0·1 mm. (Found: C, 74·8; H, 9·9. $C_{12}H_{20}O_2$ requires C, 75·0; H, 9·6%). On being demethylated with boiling concentrated hydriodic acid (15 ml.; *d* 1·7) for ½ hour, this compound (2 g.) yielded 2-(3 : 5-dihydroxy-2-methylphenyl)butane (XIV; R = Me) (1·5 g.), b. p. 130—131°/0·1 mm., which gave the di-*p*-nitrobenzoate, m. p. and mixed m. p. 164° (Found: N, 5·6. Calc. for $C_{25}H_{22}O_8N_2$: N, 5·9%).

Reduction of (A) *and* (B) *with Hydriodic Acid and Phosphorus.*—(A) or (B) (5 g.) was heated under reflux with hydriodic acid (75 ml.; *d* 1·7) and red phosphorus (2·5 g.) for 3 hours, and the cooled solution was diluted with water (150 ml.), saturated with ammonium sulphate, and extracted with ether (100 ml. × 6). The phenolic fraction was separated from the combined ethereal extracts by means of 2N-sodium hydroxide, and the alkaline liquor was saturated with carbon dioxide, and extracted with ether. Distillation of the residue left on evaporation of the ethereal extracts gave 2-(3 : 5-dihydroxy-2-methylphenyl)butane as a colourless oil (2·5 g.), b. p. 132—135°/0·2 mm., giving the same ferric reaction as the synthetical material (Found: C, 73·6; H, 9·2%). The di-*p*-nitrobenzoate separated from 90% acetic acid in glistening cream prisms, m. p. 164°, undepressed on admixture with a specimen from the synthetical phenol (Found: C, 62·7; H, 4·2; N, 5·8%).

(With F. M. Dean.) 3 : 5-*Dimethoxy*-2-*methylbenzyl Cyanide* (XIX; R = H, R_1 = CN).—The diazoketone [from 3 : 5-dimethoxy-2-methylbenzoyl chloride (5 g.) and excess of ethereal diazomethane] was dissolved in dioxan (20 ml.), and treated with 2N-ammonia (25 ml.) in dioxan (25 ml.) containing silver nitrate (0·2 g.), and the mixture kept (agitate) at 80° for 1½ hours. The liquid, which became red and deposited a silver mirror, was filtered, and evaporated in a vacuum, leaving a residue of almost pure 3 : 5-*dimethoxy*-2-*methylphenylacetamide* (XVIII) which formed colourless needles (4·6 g.), m. p. 149°, from alcohol (Found: N, 6·5. $C_{11}H_{15}O_3N$ requires N, 6·7%). The amide (3 g.) was dehydrated in boiling chloroform (100 ml.) with phosphoric oxide (2 g.) during 3 hours, and the resulting *cyanide* crystallised from light petroleum (b. p. 60—80°) in colourless needles, (1·8 g.), m. p. 66° (Found: C, 68·9; H, 6·8; N, 7·2. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9; N, 7·3%). From the residues unchanged amide (0·5—0·7 g.) was recovered.

A solution of this cyanide (6 g.) in benzene (150 ml.) was added to benzene (50 ml.) containing finely-powdered sodamide (1·5 g.) in an atmosphere of nitrogen, and the mixture gently heated under reflux. The sodio-derivative of the cyanide separated, and 25 minutes later the pasty mixture was cooled, treated with methyl sulphate (4·8 g.) in benzene (25 ml.), and heated on the steam-bath for 1 hour. On cooling the benzene liquor was washed with water, dried, and evaporated, and the residue distilled in a high vacuum, giving a product (4 g.), b. p. 135°/0·5 mm., which partly solidified. Ether (35 ml.), containing anhydrous stannous chloride (2 g.), was saturated at 0° with hydrogen chloride, and the methylated cyanide (1·5 g.) was introduced followed by more hydrogen chloride. On being kept the aldimine stannichloride separated as an oil which slowly crystallised, and 48 hours later the ethereal layer was decanted, and the residue repeatedly washed with fresh ether. A solution of the solid in water (30 ml.) was almost neutralised with 2N-aqueous sodium hydroxide, heated on the water-bath for 30 minutes, and a further small amount of aqueous sodium hydroxide added to render the reaction mixture neutral. The resulting aldehyde was isolated with ether, and on distillation obtained as a colourless oil,

b. p. 112—115°/0·2 mm., which, on treatment with semicarbazide acetate, gave an almost quantitative yield of a condensation product during 72 hours. This product formed rosettes of colourless prisms, m. p. 138°, from benzene–light petroleum (Found : C, 58·8; H, 7·2; N, 15·8. Calc. for $C_{12}H_{19}O_3N_3$: C, 58·9; H, 7·2; N, 15·9%).

A solution of the aldehydic product (0·4 g.) in ether (20 ml.) was treated with methylmagnesium iodide (from 0·2 g. of magnesium) in ether (20 ml.), and next day the mixture was heated under reflux for ½ hour, cooled, and treated with aqueous ammonium chloride. The ethereal layer was separated, washed, dried, and distilled, leaving the product as an oil which was acylated with pyridine and *p*-nitrobenzoyl chloride. Crystallised from alcohol, the resulting solid gave a p-*nitrobenzoate* in cream needles, m. p. 150—151° [Found (mean of 3 analyses) : C, 65·3; H, 6·2; N, 3·9. $C_{21}H_{23}O_6N$ requires C, 65·1; H, 6·5; N, 3·6. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%]. The alcoholic liquors from the crystallisation of this substance were evaporated by a current of air, and the residue extracted with boiling light petroleum (b. p. 60—80°), leaving a small amount of the derivative m. p. 150—151°. On cooling, the light-petroleum extract deposited pale yellow plates, and on repeated crystallisation from alcohol this material gave the *p*-nitrobenzoate of (B) in characteristic prisms, m. p. 108—109° alone or mixed with a natural specimen (Found : C, 64·5; H, 6·3; N, 3·9. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%).

2 : 4-*Dimethoxy*-6-*ethylbenzyl Cyanide* (XI; R = CN).—To an intimate mixture of 2 : 4-dimethoxy-6-ethylbenzaldehyde (1 mol.), hippuric acid (4 mols.), and sodium acetate (4 mols.) sufficient acetic anhydride was added to form a stiff paste which was then heated on the steam-bath for 3 hours, and treated with alcohol and water to decompose the excess of anhydride. On being kept the mixture deposited the *azlactone* in long silky, yellow needles, m. p. 148—149°, after having been recrystallised from alcohol; the yield was variable, the optimum being 6 g. of azlactone from 6 g. of aldehyde (Found : C, 71·0; H, 5·8; N, 4·0. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·7; N, 4·2%). The azlactone (3 g.) was hydrolysed with 10% aqueous sodium hydroxide for 8 hours, and the cooled solution saturated with sulphur dioxide, kept for 24 hours, filtered to remove benzoic acid, treated with concentrated hydrochloric acid, and heated on the steam-bath for 30 minutes. The phenylpyruvic acid (XI; R = $CO{\cdot}CO_2H$) was isolated with ether, and converted into the *oxime* (1·6 g.). Crystallised from alcohol, this derivative formed white fluffy needles, m. p. 155° (Found : C, 58·2; H, 6·6; N, 5·4. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%). Decomposition of the oxime (1·3 g.) with acetic anhydride (5 ml.) on the steam-bath for 15 minutes gave rise to 2 : 4-*dimethoxy*-6-*ethylbenzyl cyanide* which was purified by distillation in a high vacuum, and then by crystallisation from light petroleum (b. p. 60—80°), forming colourless prisms (1·2 g.), m. p. 76° (Found : C, 70·0; H, 7·2; N, 7·0. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·3; N, 6·8%).

2 : 4-*Dimethoxy*-6-*ethylphenylacetaldehyde* (XI; R = CHO).—The foregoing cyanide (2 g.) was added with vigorous agitation to a mixture of ether (40 ml.) and stannous chloride (3 g.) which had been saturated at 0° with hydrogen chloride. 48 Hours later the crystals and viscous oil left on decanting the ethereal layer were washed with ether, and dissolved in water (50 ml.), the solution was almost neutralised with sodium carbonate, and the mixture warmed on the steam-bath for ½ hour. On isolation the *aldehyde* was obtained as a colourless oil (1·2 g.), b. p. 150°/3 mm. (Found : C, 69·0; H, 7·9. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

1-(2 : 4-*Dimethoxy*-6-*ethylphenyl*)*propan*-2-*ol* (X; R = Me).—An ethereal solution of magnesium-methyl iodide (from 0·12 g. of magnesium) in ether (20 ml.) at below 0° was gradually added to the foregoing aldehyde (0·75 g.) in ether (20 ml.) cooled by an ice–salt mixture, and after having been kept at room temperature for ½ hour the mixture was treated with aqueous ammonium chloride. The ethereal layer was separated, dried, and distilled, leaving the alcohol as a colourless oil which was converted into the p-*nitrobenzoate*. This substance crystallised from alcohol in stout, bright yellow prisms (0·6 g.), m. p. 82° (Found : C, 64·4; H, 6·5; N, 3·6. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·8%).

UNIVERSITY OF LIVERPOOL. [*Received, July 16th*, 1948.]

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184. *The Chemistry of Fungi. Part V. The Constitution of Citrinin.*

By J. P. BROWN, ALEXANDER ROBERTSON, W. B. WHALLEY, and (in part) N. J. CARTWRIGHT.

Hydrogenation of citrinin is accompanied by aromatisation of the nucleus, giving rise to dihydrocitrinin which on esterification and methylation yields methyl *O*-dimethyldihydrocitrinin. On oxidation the latter compound furnished a lactone, methyl *O*-dimethylcitrinone, and the acid obtained by the hydrolysis of the carbmethoxy-group of this lactone underwent simultaneous decarboxylation and demethylation when heated with glycerol, yielding a phenolic lactone, identical with the product formed by the action of hot hydriodic acid on methyl *O*-dimethyldihydrocitrinone. On being boiled with aqueous sodium hydroxide this lactone gave rise to phenol (A) by simultaneous hydration and loss of carbon dioxide. These reactions in conjunction with the conversion of dihydrocitrinin into (VIII) by means of hydriodic acid have made it possible to deduce rational structural formulæ for the phenolic lactone (VI), methyl *O*-dimethyldihydrocitrinone (V; R = Me), *O*-dimethyldihydrocitrinin (IV; R = H), and for dihydrocitrinin (III; R = H). The expression (II) appears best to represent the properties of citrinin.

Methylation of methyl citrinin gave a complex mixture from which a crystalline compound (M), $C_{14}H_{15}O_4(OMe)$, has been isolated in comparatively small yield. On alkaline hydrolysis this substance yielded acetaldehyde, diethyl ketone, and formic acid, together with a phenolic

alcohol which is represented by (XV; R = OH) since it can be reduced to the dihydric phenol (XV; R = H). When the crude methylation product is subjected to hydrolysis there is formed, in addition to the foregoing products, a considerable amount of an acid fraction. Esterification of this material followed by oxidation of the ester gave the lactone (V; R = Me). In consequence, it is concluded that the major component of the methylation mixture is formed by addition of the elements of methanol to citrinin and aromatisation with subsequent methylation.

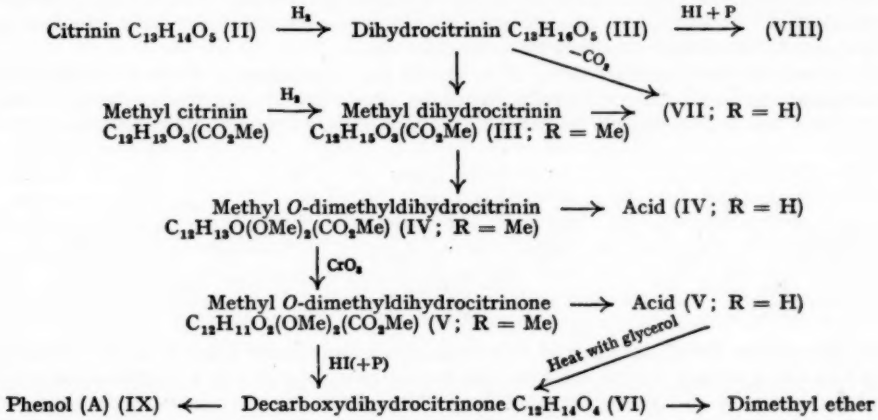
In Part IV of this series (previous paper) the phenolic hydrolysis product of citrinin, phenol (A), $C_{11}H_{16}O_3$, formed by the action of boiling dilute acids or alkalis was shown to be 3-(3 : 5-dihydroxy-2-methylphenyl)butan-2-ol (IX) and, as the only additional products in this decomposition are formic acid and carbon dioxide, the problem of developing a structure for citrinin consequently resolves itself into the question of inserting the ·CH· group eliminated as formic acid and of determining the position of the carboxyl group in the phenol (A) skeleton. In our view, leaving aside the erroneous orientation implied for phenol (A), a serious objection to the current structure for citrinin proposed by Coyne *et al.* (*Phil. Trans.*, 1931, *B*, **220**, 297) is that a compound having formula (I) would be expected to give oxalic acid and not formic acid on hydrolysis (or on ozonolysis) because the phenylglyoxylic acid, which would normally be a hydration product of (I) and thus constitute a stage in the hydrolytic fission, would not on general grounds be expected readily to undergo this kind of decomposition. In the course of attempts to obtain information contributing to a more exact knowledge of the structure of citrinin a study of the hydrogenation and methylation products of the compound was undertaken.

Although citrinin cannot be esterified under the usual conditions, the interaction of the sodium salt with methyl sulphate in aqueous sodium hydrogen carbonate has been found to give a satisfactory yield of a compound which appears to be a *methyl* ester.* The same substance is formed by treatment of citrinin for a short time with methyl iodide and potassium carbonate in boiling acetone or diethyl ketone, but with diazomethane a complex reaction appears to take place, depending to some extent on the amount of reagent employed and on the time of interaction. With less than one molecular proportion of diazomethane, however, a small yield of the methyl ester was obtained. Whilst this ester shows the expected properties and can be hydrogenated to give an almost quantitative yield of *methyl dihydrocitrinin*, the analytical results obtained with some of the specimens prepared indicate that the compound remains solvated after having been dried under the usual conditions; *e.g.*, material purified from benzene appears tenaciously to retain traces of this solvent, whilst the products from acetone have the composition approximating closely to that of a hemihydrate. On being heated at or above its melting point the ester decomposes, yielding a volatile fraction which contains methanol (isolated as the *p*-nitrobenzoate) and a complex residue from which citrinin can be separated by crystallisation. Unlike citrinin, the ester forms an unstable condensation product with acidic 2 : 4-dinitrophenylhydrazine hydrochloride which is regarded as the 2 : 4-*dinitrophenylhydrazone* of a hydrated form.

According to Hetherington and Raistrick (*Phil. Trans.*, 1931, *B*, **220**, 269), the reduction of citrinin with zinc dust and acetic acid furnished a highly unstable product from which they were able to prepare an acetyl derivative believed to be a diacetate. We have found that the hydrogenation of citrinin in methanol with hydrogen at atmospheric pressure or at 40 lb./sq. in. and a palladium–charcoal catalyst gives an excellent yield of a stable compound *dihydrocitrinin*. This substance, which is accompanied by traces of a phenol $C_{11}H_{14}O_2$ when the hydrogenation is effected at 40 lb./sq. in., and which is a stable dextrorotatory carboxylic acid giving a characteristic intense blue ferric reaction in alcohol, readily forms a *diacetate* and a methyl ester which is identical with the hydrogenation product obtained from methyl citrinin. On decarboxylation with hot glycerol, dihydrocitrinin gave rise to a dihydric phenol as an almost colourless glass which could not be induced to crystallise but was conveniently characterised by being converted into a well crystallised *di*-p-*nitrobenzoate*. This phenol, which gives a pale blue colouration with aqueous ferric chloride, was also formed by boiling dihydrocitrinin with dilute aqueous sodium hydroxide. Methylation of methyl dihydrocitrinin by the methyl

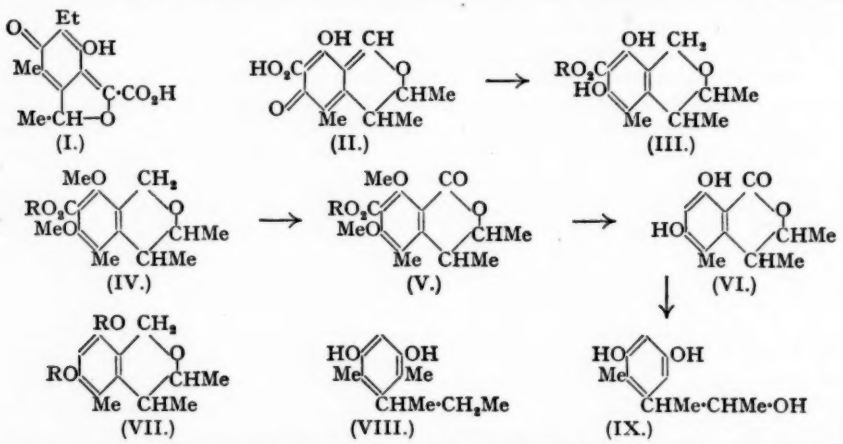
* As in the analogous case of the methyl ester of the carboxylic acid citromycetin (Part III, this vol., p. 848) we refer to the methyl ester of citrinin as methyl citrinin. The composition of trivial names for derivatives of these acids in so far as they are necessary and convenient would have been much easier and more systematic had the originators of the names followed the normal custom in naming acids, *e.g.*, citrinic and citromycetinic acid. This also applies to the more recently isolated unsaturated ketone, trichothecin (Freeman and Morrison, *Nature*, 1948, **162**, 30), for which a more appropriate name would have been, *e.g.*, trichothecenone.

iodide–potassium carbonate method gave rise to *methyl* O-*dimethyldihydrocitrinin* in good yield which on hydrolysis furnished the acid O-*dimethyldihydrocitrinin*. When methyl *O*-dimethyldihydrocitrinin, $C_{12}H_{13}O(OMe)_2(CO_2Me)$, is oxidised with chromic oxide in acetic acid it appears that a methylene group is converted into a carbonyl and a good yield of a product, $C_{12}H_{11}O_2(OMe)_2(CO_2Me)$, is obtained. The same compound is produced, but in considerably smaller yield, when aqueous potassium permanganate is employed as the oxidising agent. For convenience we have named this substance *methyl* O-*dimethyldihydrocitrinone*. Hydrolysis of the ester group in this compound yields the corresponding dextrorotatory *acid*, which, like the parent ester, resists reduction by the method of Clemmensen or by means of hydrogen and a palladium–charcoal catalyst and does not yield derivatives with carbonyl reagents. On being heated with glycerol at 250—260°, this acid underwent simultaneous decarboxylation and demethylation, yielding a dihydroxyphenolic lactone *decarboxydihydrocitrinone*, identical with the product formed by the action of boiling hydriodic acid on *O*-dimethylhydrocitrinone or its methyl ester. This compound was readily converted into a *dimethyl ether*, and the behaviour of this derivative with aqueous and alcoholic sodium hydroxide clearly indicated that the ether and consequently the parent substance contained a lactone group. In agreement with the lactone structure it was found that on being boiled with dilute aqueous sodium hydroxide the phenolic acid, formed as the sodium salt by the opening of the lactone ring in decarboxydihydrocitrinone, readily lost carbon dioxide, yielding the phenol (A) (IX). The foregoing degradations and transformations of citrinin may be conveniently summarised in the accompanying table :



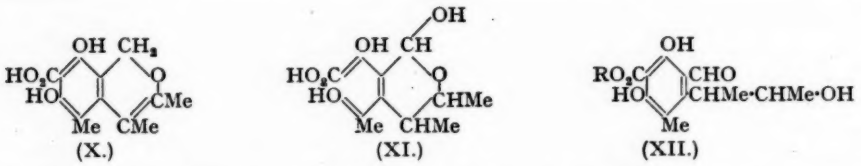
From its properties and ready conversion into phenol (A) (IX) by a simultaneous hydration and decarboxylation process in agreement with the expected behaviour of a β-resorcylic acid, it is clear that decarboxydihydrocitrinone has the structure (VI) and, since this substance is in turn derived from *O*-dimethyldihydrocitrinone by a simultaneous demethylation and decarboxylation process, it follows that the latter compound may be formulated as (V; R = H) and its methyl ester as (V; R = Me). Further, methyl *O*-dimethyldihydrocitrinone is formed by the oxidation of a methylene group in methyl *O*-dimethyldihydrocitrinin to a carbonyl group and, since the latter is lactonic and not ketonic and because of the fact that the parent dihydrocitrinin does not contain a free alcoholic hydroxyl group, it is clear that the oxidation involves the conversion of a $\cdot CH_2\cdot O\cdot C\!:$ residue into $\cdot CO\cdot O\cdot C\!:$, and therefore methyl *O*-dimethyldihydrocitrinin may be represented by formula (IV; R = Me) and the parent acid by (IV; R = H). Hence dihydrocitrinin and its methyl ester have formulæ (III; R = H) and (III; R = Me), respectively. The latter structure is in agreement with the important observation that on being boiled with hydriodic acid and red phosphorus dihydrocitrinin is converted, presumably by way of (VII; R = H), into the dihydric phenol 2-(3 : 5-*dihydroxy*-2 : 6-*dimethylphenyl*)*butane* (VIII), identified by comparison of the *di*-p-*nitrobenzoate* with a synthetical sample. With regard to the position of the carboxyl group in dihydrocitrinin (III; R = H), and consequently in (IV; R = H) and (V; R = H), it may be noted that (III; R = H) and (III; R = Me) give intense alcoholic ferric reactions, indicating that the carboxyl and the carbmethoxy-group are in the *o*-position to a phenolic hydroxyl group. The blue colouration of the acid (III; R = H) is in keeping with the compound being a γ-resorcylic derivative, *i.e.*, *p*-orsellinic acid type. On the other hand, the decarboxylation product (VII;

R = H) from dihydrocitrinin gives a faint blue ferric reaction with the aqueous reagent but, as would be expected in the absence of a carbonyl group in the *o*-position to a hydroxyl,



the substance gives a negative reaction with alcoholic ferric chloride. In contrast with the latter compound (VII; R = H) and in keeping with the structure allocated to it, the lactone (VI) gives a violet colouration with alcoholic ferric chloride.

On the basis of the structure (III; R = H) for dihydrocitrinin and the assumption that the aromatisation involves only a rearrangement of bonds simultaneously with the addition of hydrogen and not a deep-seated fundamental intramolecular change, a constitution for citrinin



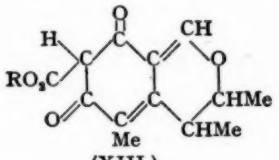
may be derived by the abstraction of two hydrogen atoms from (III; R = H). This may be done in two ways, giving rise to either (*a*) the *iso*chromen type (X) or a modification containing a vinyl group or (*b*) the hemiquinonoid type (II). Of these alternatives the former type is excluded for two main reasons—because the structure does not contain an asymmetric carbon atom (the presence of a vinyl group would allow this but would imply easy racemisation and give rise to formaldehyde on ozonolysis) and because the formation of formic acid both on the hydrolysis and on the ozonolysis of citrinin or its methyl ester cannot be satisfactorily explained on the basis of a formula type (X). On the other hand we regard the alternative expression (II), first advanced by us (*Nature*, **1948**, **162**, 72), as best representing the chemical behaviour of citrinin because, *e.g.*, it allows for the optical activity of the compound which persists in dihydrocitrinin and its degradation products down to and including phenol (A) (IX). Further, formula (II) affords a rational explanation of the production of formic acid on ozonolysis unaccompanied by easily detectable amounts of formaldehyde. The hydrolysis with simultaneous aromatisation of the system together with the extrusion of the carboxyl group and of the potential formyl group as formic acid is obviously initiated by the addition of the elements of water at the 1 : 6-positions of the hemiquinonoid residue to give type (XI) comparable with the hydration or methosulphate addition in the case of an anhydronium base (compare Armit and Robinson, *J.*, **1925**, **127**, 1604). The hemiacetal system of (XI) then presumably changes over to give the formyl system as in (XII; R = H). That this aromatisation is accompanied by the extrusion of the formyl and carboxyl groups is not unexpected in view of the fact that the potential benzenoid system is fully substituted and, further, the expulsion of the formyl group in warm acid media finds analogy in the case of other polyhydroxy-aldehydes. The final stages in the biological formation of citrinin may well be the reversal of this hydration process, passing from the aldehydo-form (XII; R = H) to (II) by way of (XI). A laboratory synthesis of citrinin along these lines is being explored.

On the basis of formula (II) for citrinin, we regard the 2 : 4-dinitrophenylhydrazone formed

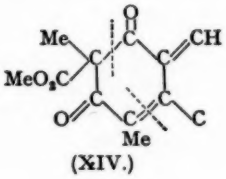
by methyl citrinin as being derived from the hydrated aromatic form (XII; R = Me) and believe that the decomposition of this compound in solution is associated with the tendency of the system (type XII) to revert to the citrinin system type (II).

For the purpose of obtaining further evidence in support of the structure (II) advanced for citrinin, the methylation of methyl citrinin and the degradation of the product were studied. In the first instance, on account of the milder nature of the reaction involved, the methylation of the ester was carried out by the methyl iodide–potassium carbonate method in boiling acetone, but the time required for the completion of the methylation process as tested for by the ferric reaction was unexpectedly long and the final product proved to be a mixture containing two main components of which only one could be isolated in the pure state. From the viscous methylation product, which had been distilled in a high vacuum, a crystalline *compound* (M) was separated in comparatively poor yield by means of solvents, but the methoxyl content of this substance, which was completely insoluble in cold aqueous sodium hydroxide, appeared to be slightly lower than that of the initial ester. The substance (M), which has a negative ferric reaction, does not appear to contain a reactive carbonyl group and on hydrolysis with boiling 28% aqueous potassium hydroxide gave rise to a mixture of acetaldehyde, diethyl ketone, formic acid, and a crystalline lævorotatory *phenol*, $C_{12}H_{18}O_3$, together with a comparatively small amount of a liquid acid which was not further investigated. On methylation, the phenol furnished a *dimethyl ether*, $C_{12}H_{16}O(OMe)_2$, in which the third oxygen atom was shown to be present in an alcoholic group by the formation of a well-crystallised p-*nitrobenzoate* of the ether. Thus in its properties the phenolic alcohol, $C_{12}H_{18}O_3$, is strictly analogous to phenol (A), $C_{11}H_{16}O_3$, and like the latter it gave rise to a liquid dihydric phenol, $C_{12}H_{18}O_2$, on reduction with hydriodic acid and red phosphorus which was characterised by being converted into the *di*-p-*nitrobenzoate*. From the analogy with phenol (A) (IX) and the fact that the di-*p*-nitrobenzoate of phenol $C_{12}H_{18}O_2$ was isomeric and not identical with the *di*-p-*nitrobenzoate* of 2-(3 : 5-dihydroxy-2 : 6-dimethylphenyl)butane (VIII) from dihydrocitrinin, it seemed reasonably certain that the parent phenol, $C_{12}H_{18}O_3$, from (M) was 3-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butan-2-ol (XV; R = OH), a conclusion which was finally established by the synthesis of the di-*p*-nitrobenzoate of (XV; R = H), identical in all respects with the natural derivative.

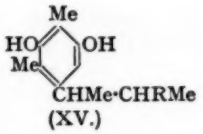
Although, owing to lack of sufficient crystalline material, we have not yet completed our investigations on the structure of (M), it seems reasonably certain from the methoxyl estimations that this compound is not an *O*-methyl ether of methyl citrinin but in all probability arises by the *C*-methylation of this ester. As a variation of the structure type (II), citrinin and its ester may exist in the ketonic forms (XIII; R = H) and (XIII; R = Me) and thus (M) may well be the *C*-methyl derivative (XIV) which could undergo hydrolytic fission with concentrated



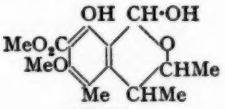
(XIII.)



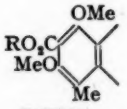
(XIV.)



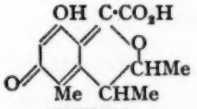
(XV.)



(XVI.)



(XVII.)



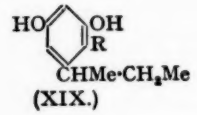
(XVIII.)

alkalis in several ways. In the formation of the chief hydrolytic product (XV; R = OH) the fission would seem to follow in the main the course taken by citrinin under similar conditions, in agreement with the fact that both compounds are in the same state of oxidation, *i.e.*, the extrusion of the potential formyl group, the hydrolysis of the carbomethoxy-group with the loss of carbon dioxide, and simultaneous aromatisation of the system. The only difference between the phenolic end products (IX) and (XV; R = OH) respectively from citrinin and from (M) is in the presence of the *C*-methyl group ultimately retained in the 4-position of (XV; R = OH). The minor products of hydrolysis, *viz.*, acetaldehyde and diethyl ketone, would seem to arise by the fission taking alternative courses; *e.g.*, the ketone in all probability arises by the initial fission of (M) proceeding as indicated by the dotted lines in formula (XIV), whilst a modification of this route could conceivably lead to acetaldehyde. Because of the difficulty at an earlier stage of

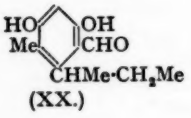
reconciling the analytical results with feasible structures for (M), careful consideration was given to the question of citrinin derivatives condensing with acetone in the presence of potassium carbonate during the methylation process, thus leading to an addendum responsible for acetaldehyde and diethyl ketone. Apart from other factors, however, the amounts of the latter products isolated as their 2 : 4-dinitrophenylhydrazones do not justify further consideration of this view, and, morover, it was subsequently found that when acetone was replaced by methanol as the solvent in the methylation procedure the same results were obtained.

When the distilled mixed methylation product from methyl citrinin was hydrolysed under the conditions subsequently applied to substance (M), there was formed, in addition to the products obtained from (M), a comparatively large amount of an acid fraction which did not yield crystalline material and could not be distilled unchanged in a high vacuum. This acidic fraction was esterified by means of ethereal diazomethane but it was not possible to effect a satisfactory purification of the product by fractional distillation in a high vacuum. Oxidation of the distilled material with chromic oxide in acetic acid, however, gave rise to a comparatively good yield of a crystalline ester which was found to be identical in every way with methyl *O*-dimethyldihydrocitrinone (V; R = Me), giving *O*-dimethyldihydrocitrinone (V; R = H) on hydrolysis. Similar results were obtained when, before attempting to separate crystalline compound (M), the methylation product was distilled and subjected to oxidation with chromic oxide and the resulting mixture hydrolysed with boiling 28% aqueous potassium hydroxide. Under these conditions the products obtained were acetaldehyde, diethyl ketone, formic acid, the phenol (XV; R = OH), and *O*-dimethyldihydrocitrinone (V; R = H); the aldehyde and ketone were formed in comparatively small amounts as in the case of (M). It would thus appear that the second major product of the methylation process, which on oxidation gives rise to (V; R = Me), and on hydrolysis is not degraded like (M), contains methyl groups on the nuclear oxygen atoms, and consequently we may consider the first step in the formation of this methylation product to be the addition of the elements of methyl alcohol to methyl citrinin with simultaneous aromatisation to give substance (XVI). The latter intermediate is considered to undergo subsequent methylation, yielding the dimethyl ether (XVII; R = Me), and it is this substance which is oxidised, giving rise to methyl *O*-dimethyldihydrocitrinone (V; R = Me). A concentrate consisting largely of the ether believed to be (XVII; R = Me) has been obtained after the separation of crystalline (M), but this material is still contaminated with the latter because on hydrolysis it gives small amounts of the hydrolytic products characteristic of (M) as well as a high proportion of (XVII; R = H).

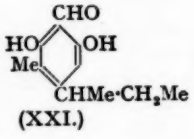
When the methylation of methyl citrinin was carried out in methyl alcohol instead of in acetone a similar mixed product was obtained, as shown by hydrolysis, but the amount of (M) present appears to be less than in the acetone product.



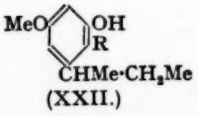
(XIX.)



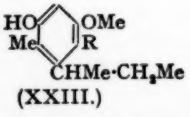
(XX.)



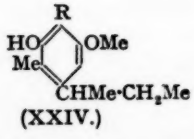
(XXI.)



(XXII.)



(XXIII.)



(XXIV.)

In the synthesis of the phenol (VIII) obtained from dihydrocitrinin, the Gattermann reaction was applied to the resorcinol derivative (XIX; R = Me), but in place of the expected aldehyde (XX) as the sole product of the reaction, we obtained a mixture consisting mainly of the isomeric *γ-aldehyde* (XXI) accompanied by only small amounts of the required compound. The orientation of (XXI) was deduced in the first instance from its resemblance to *m*-xylorcylaldehyde (Robertson and Robinson, *J.*, 1927, 2196) in having a bright yellow colour and in giving an intense bottle-green colouration with alcoholic ferric chloride. On reduction by Clemmensen's method this aldehyde (XXI) gave rise to 2-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butane (XV; R = H), which was characterised by the formation of the di-*p*-nitrobenzoate, identical in every respect with the corresponding derivative of the phenol (XV; R = H) prepared by the degradation of compound (M) by way of (XV; R = OH). When, however, the mixed product from the Gattermann reaction, which had been distilled in a

vacuum once, was subjected to the Clemmensen reaction and the product acylated with *p*-nitrobenzoyl chloride and pyridine, it was possible to isolate a much less soluble di-*p*-nitrobenzoate, identical with the corresponding derivative of the phenol (VIII) from dihydrocitrinin. The absolute orientations of the isomeric aldehydes (XX) and (XXI) and consequently those of the phenols (VIII) and (XV; R = H) were established in the following way. The aldehyde (XIX; R = CHO) was converted into the monomethyl ether (XXII; R = CHO) which was characterised by the formation of the *semicarbazone*. The orientation of this ether (XXII; R = CHO) follows from the fact that it gives an intense ferric reaction in alcohol and reacts with acetophenone in the presence of hydrogen chloride in ethyl acetate to give a flavylium salt. On reduction by the Clemmensen method this monomethyl ether (XXII; R = CHO) yielded 2-(3-hydroxy-5-methoxy-2-methylphenyl)butane (XXII; R = Me), characterised by the formation of the p-*nitrobenzoate*. Application of the Gattermann reaction to the latter ether gave rise to the expected mixture of aldehydes (XXIII; R = CHO) and (XXIV; R = CHO), which were conveniently separated by taking advantage of the fact that 2-(3-*hydroxy*-5-*methoxy*-6-*formyl*-2-*methylphenylbutane* (XXIII; R = CHO), in agreement with its orientation, is readily extracted from an ethereal solution of the mixed reaction product by means of 0·5% aqueous sodium hydroxide, leaving the isomeride (XXIV; R = CHO) in the solvent. On reduction (XXIII; R = CHO), which did not give a ferric reaction, furnished the monomethyl ether (XXII; R = Me) and on demethylation this derivative yielded (VIII), characterised by being converted into the di-*p*-nitrobenzoate, identical with the product obtained from dihydrocitrinin, and by the reduction of the crude mixture of the aldehydes (XX) and (XXI). 2-(3-Hydroxy-5-methoxy-4-formyl-2-methylphenyl)butane (XXIV; R = CHO), which was characterised by the formation of the *semicarbazone*, gave the expected intense ferric reaction in alcohol, and a flavylium chloride on being condensed with acetophenone by means of hydrogen chloride. On reduction the aldehyde furnished the monomethyl ether (XXIV; R = Me). Demethylation of the latter compound gave rise to (XV; R = H), the di-*p*-nitrobenzoate of which was identical in every way with the derivative obtained from the compound (XV; R = OH) by way of (XV; R = H).

Addendum.—In view of the communication by Gore *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 2287) proposing an alternative structure (XVIII) for citrinin, to which our attention was directed after the present memoir had been prepared, it seems desirable to summarise the available evidence which we believe proves that the carboxyl group is attached directly to the potential aromatic kernel as in (II) and not to a side chain of it as in (XVIII) :

(*a*) The formation of formic acid and not oxalic acid by citrinin, methyl citrinin, and its methylation product (M) on hydrolysis.

(*b*) The production of formic acid and not oxalic acid by the ozonolysis of citrinin, methyl citrinin, and mixed methylation product and the failure to obtain formic acid from dihydrocitrinin and its derivatives by this means.

(*c*) The oxidation of methyl *O*-dimethyldihydrocitrinin to a lactone without loss of the carbomethoxy-group together with the subsequent conversion of the product into the lactone (VI) by loss of this group.

(*d*) The failure to convert dihydrocitrinin by heating into a lactone (α-keto-dihydrofuran type) which would be expected on the basis of formula (XVIII).

(*e*) The intense alcoholic ferric reactions given by dihydrocitrinin and its methyl ester are in keeping with formulæ (III; R = H) and (III; R = Me) but not with a dihydro-derivative of (XVIII).

Experimental.

Methyl Citrinin.—The citrinin employed in this investigation was obtained from *Penicillium citrinum* [A.D. 23 (Baarn)] grown on the glucose medium employed by Hetherington and Raistrick, (*loc. cit.*). The acid, which can be sublimed unchanged in a high vacuum, has been found to have m. p. 178—179° (decomp.) after repeated crystallisation from methanol, $\lambda_{min.}$ ~235 mμ, $E^{1\%}_{1\,cm.}$ ~309; $\lambda_{max.}$ ~250 mμ, $E^{1\%}_{1\,cm.}$ ~333; $\lambda_{min.}$ ~285 mμ, $E^{1\%}_{1\,cm.}$ ~66; $\lambda_{max.}$ ~331 mμ, $E^{1\%}_{1\,cm.}$ ~266 with inflexions at λ ~371, ~390, ~481 mμ (Hetherington and Raistrick give m. p. 169°, decomp.). Repeated attempts under a variety of conditions to effect the decarboxylation of citrinin and obtain decarboxycitrinin have failed.

A well agitated solution of citrinin (5 g.) in saturated aqueous sodium hydrogen carbonate (100 ml.), maintained at 45—50°, was treated with methyl sulphate (25 ml.) with the further addition of sodium hydrogen carbonate as required to keep the reaction mixture neutral (Congo-red); 45 minutes later more methyl sulphate (12 ml.) and aqueous sodium hydrogen carbonate as required were added and, after a further 45 minutes, the solid ester (3·8 g.) was collected, washed, dried, and crystallised from benzene and then acetone, forming colourless, flat, stout, diamond-shaped prisms, m. p. 138° (decomp.), $[\alpha]_D^{20°}$ +96·9° (*c*, 1·878 in chloroform), $\lambda_{min.}$ ~240 mμ, $E^{1\%}_{1\,cm.}$ ~150; $\lambda_{max.}$ ~260 mμ, $E^{1\%}_{1\,cm.}$ ~450; $\lambda_{min.}$ ~285 mμ, $E^{1\%}_{1\,cm.}$ ~11; $\lambda_{max.}$ ~335 mμ, $E^{1\%}_{1\,cm.}$ ~140, giving an olive-green colouration with alcoholic

ferric chloride [Found, in material crystallised from acetone and dried over phosphoric oxide at room temperature: C, 61·9; H, 5·9. Found, in specimen dried in a high vacuum at 60° for 2 hours: C, 62·1; H, 6·0; OMe, 10·9. Found, in specimen crystallised from benzene: C, 63·1; H, 6·8. Found, in same material dried in a high vacuum at 80° for 2 hours: C, 63·2; H, 6·9. $C_{13}H_{13}O_4(OMe)$ requires C, 63·6; H, 6·1; OMe, 11·7%. $C_{13}H_{13}O_4(OMe),0{\cdot}5H_2O$ requires C, 61·5; H, 6·2; OMe, 11·4%]. Acidification of the aqueous sodium hydrogen carbonate liquor left on separation of the ester gave unchanged citrinin (approx. 0·7 g.).

The same ester mixed with much gummy material was formed when a solution of citrinin (2 g.) in chloroform (25 ml.) and methanol (25 ml.) was mixed with ethereal diazomethane (0·6 mol. of diazomethane), kept for 15 minutes, and evaporated. The residual product was extracted with ether, the extract was washed with aqueous sodium carbonate, dried, and evaporated, and the residual oil was dissolved in a little warm benzene. On being kept, the solution slowly deposited the methyl ester (0·2 g.), m. p. 138° (decomp.), identical with a specimen prepared by the methyl sulphate method.

A solution of citrinin (6 g.) in acetone (150 ml.) and methyl iodide (10 ml.) was boiled with potassium carbonate (12 g.) for 24 hours with the addition of more iodide (5 ml.) and carbonate (3 g.) after 12 hours. The voluminous yellow solid was collected, washed with acetone, dissolved in warm water (300 ml. at 50°), and decomposed with dilute hydrochloric acid, yielding the colourless ester. This compound was collected, dried, and crystallised from benzene, forming diamond-shaped prisms, m. p. and mixed m. p. 137° (decomp.) (Found, in material dried at 60° in a high vacuum: C, 63·2; H, 6·8; OMe, 10·3%). When the acetone was replaced by diethyl ketone the same ester, m. p. and mixed m. p. 137° (decomp.), was obtained. On distillation in a high vacuum the residue left on evaporation of the acetone filtrate from the sodium salt gave a colourless neutral oil, b. p. 130—140°/0·3 mm., which had a negative ferric reaction and did not react with carbonyl reagents. The analogous product obtained when diethyl ketone was employed in the methylation process was a pale yellow oil, b. p. 130—140°/0·2 mm., having a negative ferric reaction and forming a 2 : 4-dinitrophenylhydrazone, red needles from acetic acid (Found: C, 57·9; H, 5·1; N, 14·1%).

The methyl ester of citrinin is sparingly soluble in hot alcohol, moderately soluble in chloroform, and insoluble in light petroleum. When the ester (0·5 g.) was heated under reflux with 5N-sulphuric acid (25 ml.) for 1 hour the almost clear solution was found to contain formic acid, identified by distillation of a portion and the isolation of the acid as *NN'*-diphenylformamidine hydrochloride (Whalley, *J.*, 1948, 1015). From the remaining portion of the solution, phenol (A) was isolated with ether. Similarly, when the ester (0·5 g.) was heated under reflux with 2N-aqueous sodium hydroxide (25 ml.) for 1 hour, formic acid and phenol (A), m. p. and mixed m. p. 128°, were obtained from the acidified hydrolysate. When a specimen of the ester (1·8 g.), which had been dried in a desiccator at room temperature, was heated to 130—140° in a slow current of nitrogen for ½ hour and the effluent gas passed through a trap cooled with solid carbon dioxide, a small amount of benzene was obtained, originally present as solvent of crystallisation. The residue contained, *inter alia*, citrinin (0·6 g.) and a small amount of a product exhibiting ketonic properties. In another experiment the effluent gas was passed into a mixture of pyridine and *p*-nitrobenzoyl chloride, and from the latter methyl *p*-nitrobenzoate, m. p. 96°, was then isolated and identified by comparison with an authentic specimen.

A mixture of methyl citrinin (0·6 g.), prepared by either method, in methanol (50 ml.), containing 2 : 4-dinitrophenylhydrazine (1 g.) and concentrated sulphuric acid (2·5 ml.), was kept at room temperature for 24 hours. The addition of water (50 ml.) to the mixture gave a yellow precipitate (0·6 g.) which, on being chromatographed from chloroform on alumina, was found to be homogeneous, being eluted with chloroform–methanol. Repeated crystallisation of this 2 : 4-*dinitrophenylhydrazone* from alcohol tended to cause decomposition. For analysis, the substance was purified from warm methanol, forming slender yellow needles, m. p. 165—166° (decomp.) [Found: C, 52·2; H, 4·8; N, 12·3; OMe, 6·3. $C_{19}H_{19}O_8N_4(OMe)$ requires C, 52·0; H, 4·8; N, 12·1; OMe, 6·7%]. On being boiled for a short time with alcohol, the 2 : 4-dinitrophenylhydrazone partly decomposed. Treatment of the alcoholic filtrate from the unchanged hydrazone with an excess of alcoholic 2 : 4-dinitrophenylhydrazine sulphate regenerated the derivative.

Dihydrocitrinin (III; R = H).—Citrinin (5 g.) was hydrogenated in methanol (200 ml.) with hydrogen at 40 lb./sq. in. and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) in the course of 1½ hours. After the removal of the catalyst by filtration, the solution rapidly assumed a bluish tinge which changed to green when the liquor was kept for several days. The product left on evaporation of the solution under diminished pressure was triturated with benzene and crystallised from the same solvent and then from benzene–acetone, giving *dihydrocitrinin* in small colourless prisms (4·2 g.), m. p. 171°, $[\alpha]_D^{18°}$ +18·3° (*c*, 2·981 in chloroform), $\lambda_{min.}$ ~240 mμ, $E^{1\%}_{1\,cm.}$ ~250; $\lambda_{max.}$ ~260 mμ, $E^{1\%}_{1\,cm.}$ ~400; $\lambda_{m'n.}$ ~285 mμ, $E^{1\%}_{1\,cm.}$ ~10; $\lambda_{max.}$ ~330 mμ, $E^{1\%}_{1\,cm.}$ ~100 [Found: C, 62·0; H, 6·4; *M* (by titration), 251·7. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%; *M*, 252). This compound, which is also obtained when the hydrogenation is carried out at atmospheric pressure, gives an intense Prussian-blue colouration with ferric chloride in water or alcohol, and is sparingly soluble in benzene or light petroleum, and readily soluble in alcohol, acetone, or chloroform. Acetylation of dihydrocitrinin (0·8 g.) with acetic anhydride (3 ml.) and pyridine (1 ml.) at room temperature for 36 hours gave the *diacetate* (0·8 g.), which separated from benzene in colourless prisms, m. p. 144—145°, readily soluble in aqueous sodium hydrogen carbonate, alcohol, or acetone and having a negative ferric reaction (Found: C, 60·8; H, 5·9. $C_{17}H_{20}O_7$ requires C, 60·7; H, 6·0%).

From the benzene liquor left from the purification of about 50 g. of dihydrocitrinin a small amount of a second crystalline, non-acidic, phenolic product (0·5 g.) was obtained. Recrystallised from benzene–acetone, this substance formed colourless prisms, m. p. 188°, insoluble in water, chloroform, or light petroleum and soluble in acetone or alcohol, and giving a pale green ferric reaction in alcohol (Found: C, 74·1, 73·8; H, 7·9, 7·7. Calc. for $C_{11}H_{14}O_3$: C, 74·2; H, 7·9%).

A solution of dihydrocitrinin in ether was treated with slightly more than one molecular proportion of ethereal diazomethane, and 10 minutes later the unchanged reagent was destroyed with a little

hydrochloric acid. Slow evaporation of the solution in the course of 7 days gave the crystalline *methyl* ester (III; R = Me). Recrystallised from light petroleum (b. p. 40—60°), this derivative formed large colourless prisms, m. p. 60°, soluble in the usual organic solvents except light petroleum and giving a violet colouration with alcoholic ferric chloride and a weak blue with the aqueous reagent, in which the substance is but sparingly soluble [Found: C, 63·0; H, 6·5; OMe, 11·6. $C_{13}H_{15}O_4(OMe)$ requires C, 63·2; H, 6·8; OMe, 11·6%]. Acetylation of this ester (1·5 g.) with acetic anhydride (8 ml.) and pyridine (10 ml.) on the water-bath for ½ hour and subsequent dilution of the cooled mixture with water and dilute hydrochloric acid gave the *diacetate*, which formed colourless needles (1·7 g.), m. p. 114°, from aqueous methanol, having a negative ferric reaction (Found: C, 61·7; H, 6·5. $C_{18}H_{22}O_7$ requires C, 61·7; H, 6·3%). This compound (0·5 g.) was recovered unchanged after having been heated under reflux with acetic anhydride (8 ml.) and sodium acetate (0·3 g.) for 1 hour.

Hydrogenation of the methyl ester of citrinin (0·5 g.) in methanol (30 ml.) with hydrogen and a 20% palladium–charcoal catalyst (0·25 g.) for 1 hour gave the same dihydro-ester, m. p. and mixed m. p. 60°, forming the diacetate, m. p. 114°.

Decarboxydihydrocitrinin (VII; R = H).— A mixture of dihydrocitrinin (0·5 g.) and glycerol (5 ml.) was kept at 170° in an atmosphere of nitrogen for 10 minutes and then at 200° for one minute, and the product isolated from a solution of the cooled mixture in water (30 ml.) with ether. Evaporation of the extracts, which had been washed with aqueous sodium hydrogen carbonate and dried, left a very viscous liquid which did not crystallise and on distillation gave a phenol as a yellowish glass, b. p. 180°/0·1 mm., exhibiting a negative reaction with alcoholic and a pale blue-green colouration with aqueous ferric chloride and a yellow colouration with aqueous bleaching powder. On acylation with *p*-nitrobenzoyl chloride–pyridine, this product gave the *di-p-nitrobenzoate*, forming colourless needles, m. p. 160°, from acetic acid and then alcohol (Found: C, 61·8; H, 4·4; N, 5·5. $C_{34}H_{22}O_9N_2$ requires C, 61·7; H, 4·4; N, 5·5%).

Decarboxylation of dihydrocitrinin (1 g.) was also effected with boiling 2N-aqueous sodium hydroxide during 20 minutes, and the product isolated from the acidified liquor with ether, being obtained as a glass which gave the same di-*p*-nitrobenzoate, forming colourless needles, m. p. and mixed m. p. 160°, from alcohol (Found: C, 61·8; H, 4·4; N, 5·5%). When the dihydric phenol was methylated by the methyl iodide–potassium carbonate method the alkali-insoluble product did not form a *p*-nitrobenzoate.

O-*Dimethyldihydrocitrinin* (IV; R = H).—A solution of the foregoing methyl ester (2 g.) in acetone (150 ml.) and methyl iodide (4 ml.), containing potassium carbonate (8 g.), was heated under reflux for 18 hours, with the addition of more iodide (2 ml.) at intervals of 6 hours and 12 hours, until a test portion did not give a ferric reaction. On isolation, *methyl* O-*dimethyldihydrocitrinin* (IV; R = Me) was purified by distillation in a high vacuum and obtained as a pale yellow oil, b. p. 152—154°/0·3 mm., $[\alpha]_D^{20°}$ −19·5° (*c*, 4·692 in chloroform), which did not solidify and had a negative ferric reaction [Found: C, 65·3; H, 6·9; OMe, 25·4. $C_{13}H_{13}O_3(OMe)_3$ requires C, 65·3; H, 7·5; OMe, 31·4%]. This ester (4 g.) was hydrolysed with boiling 6% methanolic potassium hydroxide (80 ml.) for 2 hours, the greater part of the solvent was distilled off in a vacuum, the residue was treated with water (50 ml.), unchanged ester was removed by extraction with ether, and the residual alkaline solution was acidified with hydrochloric acid. The resulting O-*dimethyldihydrocitrinin* (IV; R = H) separated as an oil which solidified on trituration with water and then formed colourless prisms (3·5 g.), m. p. 124°, from ether–light petroleum (b. p. 40—60°). Recrystallised from aqueous methanol, the substance was obtained as a hydrate in large hexagonal plates, m. p. 66—68°, which on being dried in a vacuum over phosphoric oxide lost solvent of crystallisation and then had m. p. 124° [Found, in anhydrous specimen: C, 64·2, 64·4; H, 7·0, 7·1; OMe, 19·5. $C_{13}H_{14}O_3(OMe)_2$ requires C, 64·3; H, 7·1; OMe, 22·1%]. This compound has a negative ferric reaction and is readily soluble in aqueous sodium hydrogen carbonate and in the usual organic solvents except light petroleum.

Oxidation of Methyl O-*Dimethyldihydrocitrinin*.—A solution of the ester (1 g.) in acetic acid (20 ml.) was gradually treated with chromic oxide (1·5 g.) with occasional cooling to moderate the rather vigorous reaction. 20 Minutes later the solvent was distilled off in a vacuum, the residue was triturated with water (50 ml.), and the colourless solid was isolated with ether and freed from traces of acidic material by treatment with dilute aqueous sodium hydrogen carbonate followed by dilute aqueous sodium hydroxide. Crystallised from light petroleum (b. p. 60—80°), the resulting *methyl* O-*dimethyldihydrocitrinone* (V; R = Me) formed large needles (0·5 g.), m. p. 104°, $[\alpha]_D^{20°}$ +145° (*c*, 3·410 in chloroform), soluble in the usual organic solvents except cold light petroleum or water and having a negative ferric reaction [Found: C, 62·3, 62·5; H, 6·7, 6·7; OMe, 30·3. $C_{13}H_{11}O_3(OMe)_3$ requires C, 62·3; H, 6·5; OMe, 30·2%]. A small amount of an acidic by-product was sometimes obtained by acidification of the aqueous sodium hydrogen carbonate washings and on crystallisation from methanol formed colourless needles, m. p. 208°, but there was insufficient material for further purification and analysis.

Methyl *O*-dimethyldihydrocitrinin (1 g.), dissolved in acetone (70 ml.), was treated with a solution of potassium permanganate (3 g.) in water (140 ml.), added gradually (5 hours), the mixture was then cleared with sulphur dioxide, and the greater part of the acetone evaporated off in a vacuum. Isolated with ether, the product was separated from a trace of acidic material by means of sodium hydrogen carbonate and crystallised from light petroleum (b. p. 60—80°), giving methyl *O*-dimethyldihydrocitrinone in large needles (0·3 g.), m. p. 104°, identical with a specimen obtained with chromic oxide.

A mixture of the methyl *O*-dimethyldihydrocitrinone (2 g.) and methanol (30 ml.), containing potassium hydroxide (3 g.), was heated under reflux for 2 hours, the greater part of the solvent was distilled, and a solution of the residue in water was acidified with hydrochloric acid. Thus precipitated, the *acid* (V; R = H) (1·75 g.) was purified by crystallisation from benzene–acetone, forming colourless plates, m. p. 233—234° (decomp.) $[\alpha]_D^{20°}$ +141·9° (*c*, 1·691 in methanol), soluble in alcohol, chloroform, or ethyl acetate, sparingly soluble in water or benzene, and having a negative ferric reaction [Found: C, 61·2; H, 6·0; OMe, 20·5; *M* (by titration), 298, 288·4. $C_{13}H_{12}O_4(OMe)_2$ requires C, 61·2; H, 6·1; OMe, 21·1%; *M*, 294]. Esterification of this compound with diazomethane regenerated the parent ester, m. p. and mixed m. p. 104°.

Decarboxydihydrocitrinone (VI).—Simultaneous demethylation and decarboxylation of the foregoing acid was effected by heating the compound in portions of 0·5 g. with glycerol (10 ml.) at 250—260° for 10 minutes, and after the addition of water the product (from 4 g. of acid) was isolated with ether and separated into neutral, phenolic, and acidic fractions. The neutral fraction (1 g.) was an intractable gum and the acidic fraction (0·8 g.) consisted mainly of unchanged acid. The viscous phenolic material (2 g.) was dissolved in ether and on slow evaporation of the solvent a crystalline phenol, *decarboxydihydrocitrinone*, m. p. 210°, separated which on recrystallisation from benzene–acetone formed colourless prisms, m. p. 214°, readily soluble in the usual organic solvents except benzene or light petroleum and having a violet ferric reaction (Found: C, 64·7; H, 6·1. $C_{13}H_{14}O_4$ requires C, 64·9; H, 6·3%). When *O*-dimethyldihydrocitrinone was heated with quinoline containing copper-bronze at 230° a small amount of an acid, m. p. 160—163°, with a red ferric reaction in alcohol and a violet in water, was obtained along with an intractable phenolic fraction which gave a violet ferric reaction and may have contained the phenol, m. p. 214°.

O-Dimethyldihydrocitrinone (1 g.) was boiled with hydriodic acid (10 ml.; *d* 1·7) and red phosphorus (1 g.) for ½ hour, and the resulting pale yellow liquor was diluted with water (30 ml.) and extracted with ether. The combined ethereal extracts were washed with aqueous sodium hydrogen carbonate and then with 2N-aqueous sodium hydroxide, and on acidification with hydrochloric acid the latter washings gave decarboxydihydrocitrinone (0·2—0·5 g.; the variable yield did not appear to depend entirely on the time of refluxing) which on purification from benzene–acetone had m. p. and mixed m. p. 215°, $[\alpha]_D^{20°}$ +99·2° (*c*, 1·533 in methanol) (Found: C, 64·7; H, 6·2%).

Methylation of the phenolic lactone (VI) (0·5 g.), dissolved in acetone (30 ml.), with methyl iodide (4 ml.) and potassium carbonate (5 g.) in the course of 10 hours gave rise to a neutral *dimethyl ether* (0·4 g.), which separated from ether in large rectangular plates or from benzene–light petroleum (b. p. 60—80°) in hexagonal plates, m. p. 138°, soluble in benzene, chloroform, or alcohol and having a negative ferric reaction (Found: C, 67·4; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). This compound, which dissolved in warm aqueous sodium hydroxide and did not separate from the cooled solution, behaved as a lactone on titration. Addition of an excess of dilute aqueous sodium hydroxide to a solution of the lactone in the minimum quantity of alcohol did not give a precipitate until the solution had been acidified with hydrochloric acid.

On treatment with *p*-nitrobenzoyl chloride (0·6 g.) and pyridine (3 ml.), decarboxydihydrocitrinone (VI) (0·2 g.) gave an almost theoretical yield of the *di*-p-*nitrobenzoate*, which formed colourless prisms, m. p. 206°, from ethyl acetate (Found: C, 59·8; H, 3·9; N, 5·4. $C_{26}H_{20}O_{10}N_2$ requires C, 60·0; H, 3·8; N, 5·4%).

Conversion of Decarboxydihydrocitrinone into Phenol (A).—A solution of this lactone (0·5 g.) in 25% aqueous potassium hydroxide (20 ml.) was boiled in an atmosphere of nitrogen for 5 hours, the cooled solution was acidified with hydrochloric acid, and the product was isolated with ether. This gummy substance was triturated with chloroform and then on crystallisation from the same solvent gave phenol (A) in almost colourless prisms, m. p. 128°, after having been sublimed at 150°/0·01 mm. to remove solvent of crystallisation, identical with an authentic specimen (Found: C, 67·3; H, 8·3. Calc. for $C_{11}H_{16}O_3$: C, 67·4; H, 8·2%). A mixture of phenol (A) (0·5 g.), diazoaminobenzene (2 g.), and alcohol (20 ml.) was warmed on the steam-bath until a clear solution was formed. On being kept at room temperature the mixture deposited the *bisphenylazo*-derivative in the course of 4 days, which then separated from alcohol in deep red needles, m. p. 204—205° (decomp.), undepressed on admixture with an authentic specimen, m. p. 204—205° (decomp.) (Found: C, 68·4; H, 6·1; N, 13·8. $C_{23}H_{24}O_3N_4$ requires C, 68·3; H, 5·9; N, 13·8%).

Oxidation of Methyl O-*Dimethyldihydrocitrinone.*—To a mixture of the compound (0·5 g.) in water (15 ml.), maintained at 80°, a solution of potassium permanganate (2 g.) in water (120 ml.) was added gradually during 4½ hours. The reaction mixture was clarified with the minimum amount of sulphur dioxide and on acidification with sulphuric acid gave the *acid-ester* (0·2—0·3 g.), m. p. 204°, which separated from water in needles, m. p. 206°, $[\alpha]_D^{20°}$ +142·6° [Found: C, 56·7; H, 5·1; *M* (by titration), 343·5. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·3%; *M*, 338]. This compound (1 g.) was heated on the steam-bath with 2N-aqueous sodium hydroxide (20 ml.), and the solution cooled, acidified with hydrochloric acid, and allowed to evaporate at room temperature. Extraction of the residue with warm acetone gave a dibasic *acid* which, on recrystallisation from a small volume of acetone, formed colourless plates (0·7 g.), m. p. 200° [Found: C, 55·6; H, 5·0; equiv. (by titration), 175·9, 174·7. $C_{15}H_{16}O_8$ requires C, 55·6; H, 5·0%; equiv., 162].

Action of Hydriodic Acid and Red Phosphorus on Dihydrocitrinin.—A mixture of the dihydro-compound (2 g.), hydriodic acid (15 ml.; *d* 1·7), acetic acid (from 10 ml. of anhydride), and red phosphorus (1 g.) was gently heated under reflux for 20 minutes, cooled, diluted with water (100 ml.), and extracted several times with ether. The combined extracts were washed with aqueous sodium hydrogen sulphite and then with aqueous sodium hydrogen carbonate, dried, and evaporated. To remove traces of iodine-containing compounds a solution of the oil in acetic acid (10 ml.) was heated with zinc dust (3 g.) on the steam-bath for 3 hours, the acetic acid was evaporated, and the residue extracted with ether. Evaporation of the washed and dried extract left a viscous oil which was twice distilled in a high vacuum, giving 2-(3 : 5-*dihydroxy*-2 : 6-*dimethylphenyl*)*butane* (VIII) as a colourless oil, b. p. 120—121°/0·1 mm. (Found: C, 74·4; H, 9·4. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%). The yield of this phenol, which gave a pale blue aqueous ferric reaction, was 1 g. from 10 g. of dihydrocitrinin. Prepared in the usual way, the *di*-p-*nitrobenzoate*, which was difficult to purify, was eventually obtained in long colourless, slender, rhombic prisms, m. p. 204—205°, after repeated crystallisation from alcohol and aqueous acetic acid alternately (Found: C, 63·3; H, 4·7; N, 6·0. $C_{26}H_{24}O_8N_2$ requires C, 63·4; H, 4·9; N, 5·7%).

Methylation of Methyl Citrinin.—A mixture of the methyl ester (10 g.), acetone (250 ml.), methyl iodide (25 ml.), and potassium carbonate was heated under reflux for 90 hours with the addition of more iodide (5 ml.) and carbonate (5 g.) at 10-hourly intervals; after this period a test portion of the product had a negative ferric reaction and was insoluble in alkali. A solution of the product in ether was washed

with 2N-aqueous sodium hydroxide and then with water, dried, and evaporated. Distillation of the residue gave an almost colourless, viscous liquid (6·5 g.), b. p. 178°/0·1 mm., which partly crystallised. Of the numerous analyses carried out on different specimens of the distilled product the following examples may be quoted: [(*a*) Found: C, 65·7; H, 7·6; OMe, 16·2. (*b*) Found: C, 64·1; H, 6·3. Calc. for $C_{13}H_{13}O_3(OMe)_3$: C, 61·9; H, 7·1; OMe, 30·0%]. When a solution of this product in light petroleum containing 2% of methanol was allowed to evaporate spontaneously during several days a small amount of a *compound* (M) separated in stout needles which on recrystallisation from the same solvent had m. p. 94°, $[\alpha]_D^{20°}$ −25·2° (*c*, 1·192 in methanol), $\lambda_{max.}$ ~230 mμ, $E_{1\,cm.}^{1\%}$ ~66; $\lambda_{min.}$ ~250 mμ, $E_{1\,cm.}^{1\%}$ ~20; $\lambda_{max.}$ ~315 mμ, $E_{1\,cm.}^{1\%}$ ~550 [Found: C, 64·6, 65·0; H, 6·4, 6·6; OMe, 8·9. $C_{14}H_{16}O_4(OMe)$ requires C, 64·7; H, 6·5; OMe, 11·2%]. Another specimen gave higher results for carbon which may have been due to solvent (Found: C, 65·7, 65·8; H, 6·7, 6·6%). Repetition of the crystallisation process with liquor from the first crop of (M) gave further (diminishing) amounts of the same compound.

The distilled mixed methylation product (5 g.) was heated under reflux with 28% aqueous potassium hydroxide (125 ml.) for 2½ hours and simultaneously a slow stream of nitrogen was passed through the apparatus. The effluent gas was bubbled through two traps containing dilute sulphuric acid solutions of 2 : 4-dinitrophenylhydrazine sulphate, and an orange precipitate gradually separated. By a combination of chromatography from chloroform and fractional crystallisation this precipitate was resolved into the 2 : 4-dinitrophenylhydrazones of acetaldehyde and of diethyl ketone. Recrystallised from methanol–light petroleum, the former formed orange-yellow needles, m. p. 162°, identical with an authentic specimen (Found: C, 43·1; H, 3·1; N, 25·2. Calc. for $C_9H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·1%). On being purified from methanol–light petroleum, the 2 : 4-dinitrophenylhydrazone of diethyl ketone was obtained in orange needles, m. p. 154°, unchanged on admixture with an authentic specimen (Found: C, 49·2; H, 5·1; N, 21·0. Calc. for $C_{11}H_{14}O_4N_4$: C, 49·6; H, 5·3; N, 21·0%). The experiment was repeated, and the effluent nitrogen passed through aqueous-alcoholic dimedone, giving the derivative of acetaldehyde, m. p. 140°, identical with an authentic specimen.

A portion of the alkaline hydrolysate (75% of total) was saturated with carbon dioxide and extracted with chloroform (75 ml. × 4). The clear yellow oil (2 g.) left on the evaporation of the combined, dried extracts was dissolved in a little chloroform and on slow evaporation of the solvent a small amount of crystalline *3-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butan-2-ol* (XV; R = OH) (0·5 g.) separated. Recrystallised from chloroform, the compound was obtained in colourless, stout prisms, m. p. 131°, $[\alpha]_D^{20°}$ −35·1° (*c*, 1·568 in methanol) (Found: C, 68·4; H, 8·3. $C_{13}H_{18}O_3$ requires C, 68·6; H, 8·6%). Considerable difficulty was experienced in the purification of this compound, which tended to separate as a glassy product. Methylation of this phenol (2 g.) with potassium carbonate (5 g.) and methyl iodide (5 ml.) in boiling acetone (100 ml.) during 12 hours with the addition of more iodide (5 ml.) after 6 hours gave a product a solution of which in ether was washed with 2N-aqueous sodium hydroxide and then with water, dried, and evaporated, leaving a pale yellow oil. Distillation of this material gave the *dimethyl ether* (1·7 g.) as an almost colourless oil, b. p. 124°/0·5 mm., having a negative ferric reaction [Found: C, 71·0; H, 8·9; OMe, 19·0. $C_{13}H_{16}O(OMe)_2$ requires C, 70·6; H, 9·2; OMe, 26·0%]. Acylation of this ether with *p*-nitrobenzoyl chloride–pyridine gave rise to a quantitative yield of the *p-nitrobenzoate*, forming pale yellow, stout prisms, m. p. 118°, from alcohol [Found: C, 64·9; H, 6·3; N, 4·1; OMe, 12·5. $C_{19}H_{19}O_4N(OMe)_2$ requires C, 65·1; H, 6·5; N, 3·6; OMe, 16·0%].

A mixture of the phenol (XV; R = OH) (3 g.), hydriodic acid (25 ml.; *d* 1·7), red phosphorus (2 g.), and acetic acid (from 10 ml. of anhydride) was heated under reflux for 3 hours, cooled, diluted with water (150 ml.), and extracted with ether (100 ml. × 3). The combined ethereal extracts were washed with sodium hydrogen sulphite, and then with sodium hydrogen carbonate, dried, and evaporated. A solution of the residue in acetic acid (15 ml.), containing zinc dust (5 g.), was heated on the steam-bath for 3 hours, the solvent evaporated in a vacuum, the residue treated with water (100 ml.), and the product isolated with ether and distilled in a high vacuum, giving 2-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butane as a colourless oil (2 g.), b. p. 130—131°/0·01 mm., with a negative ferric reaction in alcohol. Prepared in the usual way, the *di-p-nitrobenzoate* of this phenol separated from dilute acetic acid or a large volume of alcohol in almost colourless prisms, m. p. 146° (Found: C, 63·6; H, 4·9; N, 5·4. $C_{26}H_{24}O_8N_2$ requires C, 63·4; H, 4·9; N, 5·7%).

After the separation of the phenolic fraction, the hydrolysate was acidified (Congo-red) with hydrochloric acid and extracted with chloroform (100 ml. × 4). Evaporation of the combined dried extracts left an acidic pale yellow oil (2 g.) which gave a faint green ferric reaction and could not be distilled without decomposition. The acidic oil was treated with an excess of ethereal diazomethane, and the alkali-insoluble product distilled in a high vacuum, giving a colourless oil, b. p. 185°/0·1 mm. (Found: OMe, 29·0%), which regenerated the liquid acid on hydrolysis. Oxidation of the esterified material (1 g.), dissolved in acetic acid (10 ml.), by means of chromic oxide (1 g.) proceeded vigorously and was complete in about 5 minutes. On isolation and crystallisation from ether, the resulting oily product (0·8 g.) gave *methyl O-dimethyldihydrocitrinone*, m. p. 104°, identical with a specimen obtained by the oxidation of methyl *O*-dimethyldihydrocitrinin [Found: C, 62·2; H, 6·3; OMe, 29·0. $C_{13}H_{11}O_3(OMe)_3$ requires C, 62·3; H, 6·6; OMe, 30·2%].

The remaining portion of the original alkaline hydrolysate (25% of total) of the methylation product was acidified with 2N-sulphuric acid and distilled, giving an aqueous distillate containing formic acid which was identified by conversion into the *NN'*-diphenylformamidine hydrochloride in the usual manner.

When the distilled methylation product from methyl citrinin was oxidised with chromic anhydride in acetic acid and the product (1·5 g.) was hydrolysed with 28% aqueous potassium hydroxide (36 ml.) in an atmosphere of nitrogen, the volatile products gave a precipitate (0·3 g.) with aqueous 2 : 4-dinitrophenylhydrazine sulphate which was resolved into the 2 : 4-dinitrophenylhydrazones of acetaldehyde and of diethyl ketone, respectively identified by comparison with authentic specimens. From the alkaline liquor phenolic (0·3 g.) and acidic (1·0 g.) fractions were isolated. The phenol (XV; R = OH) formed

colourless, stout prisms, m. p. and mixed m. p. 131°, from chloroform. The acidic material, which partly solidified, was crystallised from ether, giving *O*-dimethyldihydrocitrinone in thick prisms (0·8 g.), m. p. and mixed m. p. 234° (Found : C, 61·2; H, 6·2; OMe, 19·6%).

The compound (M) (1·5 g.) was boiled with 28% aqueous potassium hydroxide for 2½ hours, a slow stream of nitrogen was passed through the apparatus, and the effluent gas was washed with aqueous 2 : 4-dinitrophenylhydrazine sulphate. The precipitate (0·6 g.) which formed in the wash-bottles was collected and separated into the 2 : 4-dinitrophenylhydrazones of acetaldehyde and of diethyl ketone. A portion of the alkaline hydrolysate (one-third) was acidified with sulphuric acid and distilled, and the presence of formic acid in the distillate was proved by the isolation of *NN'*-diphenylformamidine hydrochloride. The remainder of the alkaline liquor was saturated with carbon dioxide and the phenolic fraction (0·3 g. from two-thirds of the hydrolysate) was isolated with chloroform and crystallised from the same solvent, giving 3-(3 : 5-dihydroxy-2 : 4-dimethylphenyl)butan-2-ol (XV; R = OH) in stout, colourless prisms, m. p. and mixed m. p. 131°. Acidification followed by extraction of the carbonate liquor with ether gave a small amount of acidic material which was not investigated.

Ozonolysis of Citrinin.—A slow stream of ozone and oxygen was passed into a solution of citrinin (1 g.) in chloroform (75 ml.) at 0° for ½ hour, the solvent was removed in a vacuum, the brownish residue treated with water (75 ml.), and next day the clear, acidic liquor was decanted from a trace of oily material. An excess of 2 : 4-dinitrophenylhydrazine sulphate in dilute sulphuric acid was added to the aqueous solution, next day the voluminous deep red-brown precipitate (1 g.) was collected, the filtrate distilled, and the formic acid in the distillate converted into *NN'*-diphenylformamidine hydrochloride (0·75 g.). By chromatography from benzene on aluminium oxide the main constituent (0·8 g.) of the mixture of 2 : 4-dinitrophenylhydrazones was isolated and crystallised from methanol, forming deep crimson needles, m. p. 212° (decomp.) (Found : C, 53·3; H, 4·0; N, 11·5%).

Oxidised in a similar manner, methyl citrinin and the mixed methylation product gave similar yields of formic acid.

2-(3 : 5-*Dihydroxy*-4-*formyl*-2-*methylphenyl*)*butane* (XXI).—A solution of synthetical 2-(3 : 5-dihydroxy-2-methylphenyl)butane (Part IV, *loc. cit.*) (1 g.) in ether (100 ml.), containing zinc cyanide (1·5 g.), was saturated at 0° with hydrogen chloride and kept at room temperature for 48 hours. The viscous oily product, which had been repeatedly washed with ether by decantation, was dissolved in water (100 ml.) and, after having been neutralised with sodium hydrogen carbonate, the solution was warmed on the steam-bath for ½ hour. The resulting semi-solid was isolated with ether and on distillation in a high vacuum gave an aldehydic pale yellow oil (0·7 g.), b. p. 190—200°/0·001 mm., which solidified. Crystallisation of this product from benzene–light petroleum (b. p. 60—80°) gave the *aldehyde* (XXI) in long, slender, lemon-yellow prisms, m. p. 122°, easily soluble in alcohol, acetone, or ethyl acetate and having an intense bottle-green ferric reaction in alcohol (Found : C, 69·0; H, 7·5. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* formed bright orange-red needles, m. p. 271° (decomp.), from alcohol (Found : N, 14·7. $C_{18}H_{20}O_6N_4$ requires N, 14·4%). The same aldehyde was obtained from a specimen of 2-(3 : 5-dihydroxy-2-methylphenyl)butane prepared from citrinin (Part IV, *loc. cit.*).

The residue from the purification of the aldehyde (XXI), which gave a brownish ferric reaction in alcohol, did not solidify.

2-(3 : 5-*Dihydroxy*-2 : 4-*dimethylphenyl*)*butane* (XV; R = H).—The foregoing aldehyde (1 g.) was boiled with a mixture of concentrated hydrochloric acid (15 ml.) and alcohol (15 ml.) containing zinc amalgam (8 g.) for 1½ hours, and on isolation the product was distilled in a high vacuum, giving the butane as a colourless oil, b. p. 128—130°/0·01 mm., having a negative ferric reaction in alcohol and a pale blue colouration with the aqueous reagent. The di-*p*-nitrobenzoate separated from aqueous acetic acid and then alcohol in rosettes of colourless prisms, m. p. 146°, undepressed on admixture with a natural specimen (Found : N, 6·1%).

The once-distilled mixture of aldehydes (XX) and (XXI) was reduced by the same method, and the product distilled and converted into the mixed di-*p*-nitrobenzoates. On repeated crystallisation from alcohol and 75% acetic acid alternately a sparingly soluble ester was obtained in characteristic colourless, slender, rhombic prisms, m. p. 204—205°, identical with the di-*p*-nitrobenzoate of 2-(3 : 5-dihydroxy-2 : 6-dimethylphenyl)butane from dihydrocitrinin (Found : C, 63·4; H, 5·0; N, 5·9%).

2-(3-*Hydroxy*-5-*methoxy*-2-*methylphenyl*)*butane* (XXII; R = Me).—A mixture of 2-(3 : 5-dihydroxy-2-formylphenyl)butane (XIX; R = CHO) (7 g.), potassium carbonate (14 g.), methyl iodide (9 g.), and acetone (200 ml.) was heated under reflux for an hour, and a solution of the product in ether (200 ml.) was extracted with 2N-aqueous sodium hydroxide (50 ml. × 3). The combined alkaline liquors were acidified and extracted with ether (100 ml. × 5), the ethereal extracts were washed with 0·5% aqueous sodium hydroxide to remove unchanged phenol (1 g.), and then with water, dried, and evaporated, leaving the monomethyl ether, which on distillation was obtained as a colourless oil (4 g.), b. p. 108—110°/0·0001 mm. This compound, which gave a red-brown ferric reaction in alcohol, furnished a *semicarbazone*, forming very pale greenish needles, m. p. 195°, from aqueous alcohol (Found : C, 58·8; H, 7·3; N, 15·9. $C_{13}H_{19}O_3N_3$ requires C, 58·9; H, 7·2; N, 15·8%). Interaction of the aldehyde and acetophenone in ethyl acetate saturated with hydrogen chloride gave an orange-red flavylium chloride.

Evaporation of the original ethereal solution which had been exhausted with alkali left an oil (1·3 g.), having a negative ferric reaction, which appeared to be the dimethyl ether of (XIX; R = CHO).

Reduction of the monomethyl aldehyde (XXII; R = CHO) (3·5 g.) with zinc amalgam (25 g.) in boiling concentrated hydrochloric acid (25 ml.) and alcohol (25 ml.) for 1½ hours gave the butane monomethyl ether (XXII; R = Me), which on distillation was obtained as a colourless liquid, b. p. 110—114°/0·01 mm., having a negative ferric reaction in alcohol. The p-*nitrobenzoate* formed colourless prisms, m. p. 109°, from aqueous methanol (Found : N, 4·1. $C_{19}H_{21}O_5N$ requires N, 4·1%).

Gattermann Reaction with 2-(3-*Hydroxy*-5-*methoxy*-2-*methylphenyl*)*butane*.—A solution of the phenol (2·3 g.) in ether (100 ml.), containing hydrogen cyanide (5 ml.) and zinc cyanide (2·5 g.), was saturated with hydrogen chloride at 0°. 48 Hours later the crystalline product was collected, washed with ether, and hydrolysed with water (75 ml.) (neutralise the cold solution with sodium hydrogen carbonate) at

60—70° for 20 minutes. The resulting red oil was isolated with ether (75 ml. × 5) and the combined ethereal solutions were extracted with 0·5% aqueous sodium hydroxide (75 ml. × 3), washed with water, dried, and evaporated, leaving 2-(3-hydroxy-5-methoxy-4-formyl-2-methylphenyl)butane (XXIV; R = CHO) as a pale brown oil (1·5 g.) having an intense greenish-brown ferric reaction in alcohol. The *semicarbazone* formed colourless needles, m. p. 209°, from aqueous alcohol (Found: C, 60·2; H, 7·6; N, 14·8. $C_{14}H_{21}O_3N_3$ requires C, 60·2; H, 7·5; N, 15·1%). Reduction of this aldehyde (1·2 g.) with zinc amalgam (12 g.) in boiling concentrated hydrochloric acid (15 ml.) and alcohol (25 ml.) gave 2-(3-hydroxy-5-methoxy-2 : 4-dimethylphenyl)butane (XXIV; R = Me) as a colourless oil (1 g.), b. p. 102—103°/0·05 mm., which was demethylated with boiling hydriodic acid (5 ml.; *d* 1·7) and acetic acid (from 3 ml. of anhydride) during ½ hour. On isolation, the phenol (XXIV; R = H) was converted into the di-*p*-nitrobenzoate, which separated from alcohol in colourless prisms, m. p. 146°, identical in every respect with a specimen prepared by way of the aldehyde (XXI) (Found: N, 6·0%).

The combined 0·5% aqueous sodium hydroxide extracts from the crude Gattermann product were saturated with carbon dioxide and extracted with ether. Evaporation of the washed and dried extracts gave 2-(*3-hydroxy-5-methoxy-6-formyl-2-methylphenyl*)*butane* (XXIII; R = CHO), which crystallised from methanol in colourless prisms, m. p. 160° (0·4 g.), having a negative ferric reaction (Found: C, 69·9; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). Reduction of this aldehyde (0·45 g.) by the procedure used for (XXI) gave the monomethyl ether (XXIII; R = Me) (0·2 g.), b. p. 110—112°/0·01 mm., which on demethylation with boiling hydriodic acid and acetic acid furnished the phenol (VIII) (0·15 g.). The di-*p*-nitrobenzoate of this compound formed colourless, slender, rhombic prisms (0·2 g.), m. p. 204—205°, identical with the corresponding derivative of (VIII) prepared from dihydrocitrinin (Found: N, 6·0%).

The data recorded for the ultraviolet absorption spectra of citrinin, methyl citrinin (III; R = H), and (XIV) have been determined by Professor R. A. Morton of the Biochemistry Department of this University, to whom we express our thanks.

UNIVERSITY OF LIVERPOOL. [*Received, July 29th,* 1948.]

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185. *The Chemistry of Fungi. Part VI. Rosenonolactone from* Trichothecium roseum *Link.*

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From the dried mycelium of the mould grown on a Czapek–Dox medium two crystalline lactones, rosenonolactone and rosonolactone, have been isolated of which the former is produced in larger amount. Rosenonolactone is a lævorotatory, unsaturated, ketonic lactone, in all probability having empirical formula $C_{20}H_{28}O_3$, which on hydrogenation yields dihydrorosenonolactone and on treatment with alkali is transformed into *iso*rosenonolactone which on hydrogenation yields dihydro*iso*rosenonolactone identical with the alkali transformation product from dihydrorosenonolactone. Ozonolysis of rosenonolactone gives rise to an acid and formaldehyde, indicating the presence of a vinyl group. Oxidation of sodium rosenonate with potassium permanganate yielded an acid, $C_{20}H_{30}O_5$, which on decomposition with alkali gave rise to a ketone, $C_{10}H_{18}O$, and a dibasic keto-acid, $C_{10}H_{14}O_5$. The ketone has been degraded to a ketonic acid, $C_{10}H_{18}O_3$, and to an acid, $C_{10}H_{18}O_4$.

IN the course of studies on the antibiotic activity of fungi, a vigorous specimen of *Trichothecium roseum* Link was isolated in pure culture from decaying apples. This organism, which is the cause of "pink rot" in the fruit and was identified for us by Professor Joh. Westerdijk of Baarn, is known to exhibit considerable antagonistic activity towards other fungi (*e.g.*, Whetzel, *Ont. Nat. Sci. Bull.*, 1909, **5**, 3; Brian and Hemming, *J. Gen. Microbiol.*, 1947, **1**, 158), and an examination of its growth under a variety of conditions and of the metabolic products formed seemed to be of considerable interest. As a result it has been found, *inter alia*, that the mycelium of this organism grown on a simple Czapek–Dox medium contains in addition to mannitol two new water-insoluble lactonic substances, m. p. 214° and m. p. 186°, respectively, of which the former is produced in a considerably larger yield than the latter. In view of the recent communication by Freeman and Morrison (*Nature*, 1948, **162**, 30) announcing the isolation of the specific antifungal principle from the metabolic liquor of *T. roseum* Link, grown on a modified Czapek–Dox medium, we wish to record the results of our studies on the chemistry of the chief mycelial constituent, m. p. 214°, isolated in this laboratory in 1946.

The lactone, m. p. 214°, has been found to be a lævorotatory, unsaturated ketonic compound for which the analytical results, together with those of its derivatives and transformation products, indicate that the compound, for which we propose the name *rosenonolactone*, has in all probability the empirical formula $C_{20}H_{28}O_3$, although the formula $C_{19}H_{26}O_3$ is not entirely excluded. For the present we have adopted the former C_{20} formula for the lactone, which readily forms an *oxime*, a semicarbazone, and a 2 : 4-*dinitrophenylhydrazone*. On hydrogenation with hydrogen and a palladium–charcoal catalyst, the substance rapidly absorbed one molecule

of hydrogen, giving rise to a dihydro-derivative, *dihydrorosenonolactone*, $C_{20}H_{30}O_3$, which like the parent compound retains the ketonic group and yields an *oxime*, a 2 : 4-*dinitrophenylhydrazone*, and a semicarbazone. That the reactive ethylenic linkage in rosenonolactone is present in a vinyl group is shown by the fact that on ozonolysis the compound gives rise to formaldehyde and a carboxylic *acid*, $C_{18}H_{25}O_3(CO_2H)$. In the course of experiments designed to test for the presence of a lactone group in rosenonolactone, which is insoluble in aqueous sodium carbonate and in cold aqueous sodium hydroxide, it was found that, on being heated with aqueous alcoholic sodium or potassium hydroxide, the compound dissolves, forming a solution which remains clear on dilution with water before or after evaporation of the alcohol and on being kept does not deposit solid. Acidification of this solution with mineral acid gives an almost theoretical yield of the isomeric lactone, iso*rosenonolactone*, $C_{20}H_{28}O_3$, in which the keto-group is intact since the compound readily forms an *oxime* and also a 2 : 4-dinitrophenylhydrazone apparently identical with the corresponding derivatives obtained under the same conditions from the parent lactone. When the hydrolytic isomerisation is effected with a known amount of the reagent, the titration of the excess with standard acid and phenolphthalein as an indicator shows that *iso*rosenonic acid is present as a monosodium salt. By conversion of this salt into the corresponding silver salt and treatment of the latter with methyl iodide in boiling acetone, *methyl* iso*rosenonate* was obtained. *iso*Rosenonolactone retains the ethylenic bond present in the parent lactone, and on hydrogenation gives rise to a dextrorotatory dihydro-derivative, *dihydro*iso*rosenonolactone*, $C_{20}H_{30}O_3$, identical with the compound formed by the action of boiling aqueous-alcoholic sodium hydroxide on dihydrorosenonolactone, clearly showing that the ethylenic linkage is not concerned in or necessary to the conversion of rosenonolactone into its isomeride. Prepared by either route, dihydro*iso*rosenonolactone gave the same *oxime* and 2 : 4-dinitrophenylhydrazone and was converted into *methyl dihydro*iso*rosenonate* by way of the silver salt. Contrary to expectation, prolonged action of acetic anhydride–pyridine on *iso*rosenonolactone gave a product which appears to be a *monoacetyl* derivative and which on treatment with a warm aqueous-alcoholic sulphuric acid solution of 2 : 4-dinitrophenylhydrazine sulphate was deacetylated giving rise to the 2 : 4-dinitrophenylhydrazone of *iso*rosenonolactone. Similarly, dihydroisorosenonolactone yielded a *monoacetyl* derivative. In both cases these derivatives are in all probability obtained from the enolic form of the respective ketones.

On being boiled with alcoholic hydrochloric acid, rosenonolactone gives rise to two isomeric compounds (A) and (B) in addition to *iso*rosenonolactone, a reaction which presumably proceeds by way of the latter substance since under the same conditions it gives (A) and (B) along with some unchanged material. In both cases (A), which is a neutral ketonic lactone and which we have named allo*rosenonolactone*, is the main product of the reaction and only small amounts of (B) have been obtained. Unlike *allo*rosenonolactone, the latter substance is readily soluble in aqueous sodium hydroxide or sodium carbonate but does not appear to react with sodium hydrogen carbonate; so far, however, we have no evidence that the compound is phenolic. Interaction of *allo*rosenonolactone with warm alcoholic 2 : 4-dinitrophenylhydrazine reagent gives rise to a 2 : 4-dinitrophenylhydrazone identical with the compound formed from rosenono- and *iso*rosenono-lactone under the same conditions. It seems reasonably certain, therefore, that in the acid medium employed in the preparation of the 2 : 4-dinitrophenylhydrazone rosenono- and *iso*rosenono-lactone undergo isomerisation to *allo*rosenonolactone which then reacts to give the hydrazone.

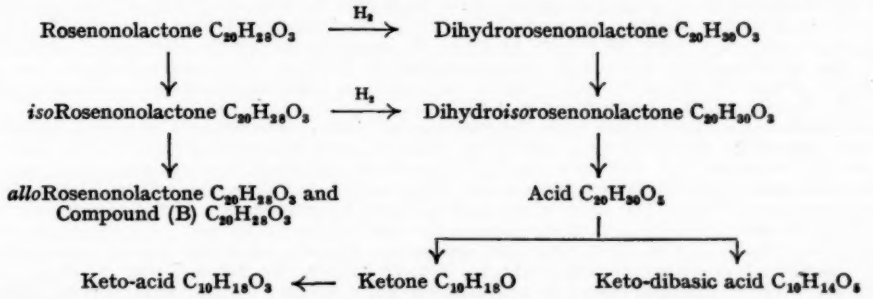
When rosenonolactone, *iso*rosenonolactone, or either of the dihydro-compounds was boiled with 50% alcoholic potassium hydroxide or fused with potassium hydroxide, traces of a volatile ketonic neutral compound were obtained which had a characteristic menthone-like odour. Similarly, oxidation of rosenono- or of *iso*rosenono-lactone gave rise to traces of the same steam-volatile odoriferous compound, which was finally obtained in quantity by the following route. Oxidation of sodium dihydro*iso*rosenonate with potassium permanganate in aqueous sodium carbonate gives rise to an *acid*, $C_{20}H_{30}O_5$, which appears to contain the carbon skeleton intact. Though we are satisfied that this acid retains at least one carbonyl group, we have not yet succeeded in isolating a stable functional ketonic derivative. On attempting to acetylate this compound by the pyridine method at room temperature, an *anhydro*-derivative, $C_{20}H_{28}O_4$, was obtained, which retains the carboxyl group of the parent substance intact, being readily soluble in aqueous sodium hydrogen carbonate. Although the parent acid appears to be reasonably stable to warm alcoholic sulphuric acid, it is gradually decomposed with warm, more slowly with cold, aqueous sodium hydroxide, giving rise to the required ketone and an *acid*. The latter compound, which forms a 2 : 4-dinitrophenylhydrazone, appears to be a dibasic acid, probably $C_{10}H_{14}O_5$, titrating potentiometrically with only one inflexion in the curve, a result

which would seem to indicate that the carboxyl groups may be symmetrically placed in the molecule and do not interfere with each other. From its composition and the absence of a double bond it appears that this acid is a cyclic compound, but a study of its constitution is reserved for a later communication. With diazomethane the compound formed a liquid neutral dimethyl ester which was readily characterised by the formation of a *semicarbazone*.

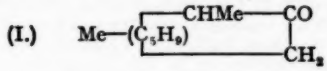
Unlike the parent acid $C_{20}H_{30}O_5$, the anhydro-compound appears to be stable to warm aqueous sodium hydroxide and does not give the ketone $C_{10}H_{18}O$.

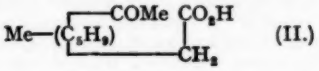
The ketonic substance $C_{10}H_{18}O$, which is isolated as a volatile oil, forms a well-crystallised *oxime* and a *semicarbazone*, the analytical results of which clearly indicate that the parent ketone has the empirical formula $C_{10}H_{18}O$. From *C*-methyl estimations on the semicarbazone, the compound probably contains at least two *C*-methyl groups and, since it appears to be saturated, it is clearly a cyclic ketone, as is suggested by its smell. In attempts to obtain further information regarding the structure of this compound, the oxime was submitted to the Beckmann rearrangement but the exact nature of the *product* has not yet been defined. Oxidation of the ketone with selenium dioxide in boiling acetic acid (but not in xylene) gave rise to a product from which a small amount of an *acid* was obtained, probably having the empirical formula $C_{10}H_{18}O_4$ rather than $C_{10}H_{16}O_4$ or $C_{10}H_{14}O_4$, a result which would seem to indicate that the oxidation has effected the opening of a ring system containing the keto-group. In this connection it may be noted that this acid gave a fluorescein reaction more closely resembling in this respect the behaviour of αβ-dimethylsuccinic acid rather than glutaric or adipic acid. On the other hand, prolonged treatment of the ketone with ozone and oxygen according to the procedure employed for *cyclo*hexanone by Stoll and Scherrer (*Helv. Chim. Acta*, 1930, **13**, 142) gave rise to an oily keto-acid which gave an iodoform reaction and was characterised by the formation of a *semicarbazone*, the analysis of which indicated that the parent keto-acid had the formula $C_{10}H_{18}O_3$.

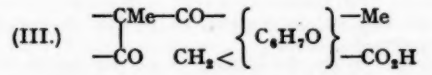
The transformations of rosenonolactone and its derivatives may be summarised as follows:

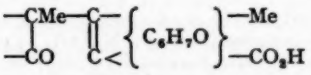


The oxidation of the cyclic ketone $C_{10}H_{18}O$ to a keto-acid $C_{10}H_{18}O_3$, giving an iodoform reaction, suggests that the parent compound may well be of the type (I) giving the oxidation product type (II). Although definite proposals regarding the mode of linking of the C_{10} residues in the acid $C_{20}H_{30}O_5$ must await the definition of the structures of these units, it would seem probable that the C_{10} residue, appearing as the keto-dibasic acid $C_{10}H_{14}O_5$ and originally









carrying the lactone system of dihydro*iso*rosenonolactone, must contain either an unreactive double bond or a dicyclic system. Further, the scission of the acid $C_{20}H_{30}O_5$ by alkalis could arise from the kind of system expressed in (III), and the dehydration of (III) to give an anhydro-compound no longer affected by warm dilute alkalis might be due to the condensation of a keto-group with an active methylene group as in (IV). In view of the fact that, like dihydro-*iso*rosenonolactone, the parent lactone and its isomeride give rise to the ketone $C_{10}H_{18}O$ on degradation, it is clear that the double bond and consequently the vinyl group in rosenonolactone are situated in the residue giving the keto-dibasic acid $C_{10}H_{14}O_5$.

From the waxy residue left after the separation of rosenonolactone from the crude mycelial

extract, a small amount of a second lactonic, slightly lævorotatory compound has been obtained, m. p. 186°, which does not appear to contain a reactive double bond or a reactive carbonyl group. For this compound, which appears to have empirical formula $C_{20}H_{30}O_3$, we propose the name *rosonolactone*, but the quantity of material available so far is insufficient for studies on its degradation.

Experimental.

Rosenonolactone.—A culture of *Trichothecium roseum* Link, syn. *Cephalothecium roseum* Corda, was isolated from a decaying apple in 1946 and stocks have been maintained on beer-wort agar slopes. In the present investigation, the cultivation of this mould, the growth of which is stimulated by the presence of corn-steep liquor or extract of peas in the medium, was studied with a view to producing optimum yields of the two crystalline metabolic products which had been isolated from the dried mycelium in the course of preliminary experiments. It was ultimately decided that the most satisfactory yields were obtained by employing the simple Czapek–Dox medium (pH 4·2) composed of sodium nitrate (2 g.), potassium chloride (0·5 g.), magnesium sulphate (0·5 g. of heptahydrate), ferrous sulphate (0·01 g. of heptahydrate), potassium dihydrogen phosphate (1 g.), and glucose (30 g.) in tap-water (1 l.) and inoculating with an aqueous suspension of spores produced on beer-wort agar. A thin mat of mycelium was grown on a shallow layer of medium (150 c.c. over an area of about 25 sq. cm.) at room temperature (15—18°) during 14 days, fresh sterile medium was added to make up the volume to approximately 1 l., and then growth was allowed to proceed at room temperature for a further 3 weeks. The faintly pink mycelium, coloured salmon-pink on the lower side, was collected, washed, dried, powdered, and extracted in a Soxhlet apparatus with ether; the yield of dried mycelium per l. of medium was 5·8—6·5 g., from which approximately 0·217 g. of the rosenonolactone was obtained. After having been exhaustively extracted with ether, a sample of the mycelium was extracted with acetone and on evaporation of the solvent mannitol was obtained, forming needles, m. p. 166°, from aqueous alcohol or acetone, identical with an authentic sample. The hexa-acetate had m. p. and mixed m. p. 122°. Subsequently it was found that the mould could be cultivated directly on deeper layers of medium.

The product (mixed with fatty material) obtained by evaporation of the ethereal extracts was warmed with alcohol, and the insoluble rosenonolactone collected. Recrystallised from benzene and then alcohol or from benzene only, this compound formed colourless squat prisms, m. p. 214°, $[\alpha]_D^{20°}$ −107·5° (*c*, 1·2 in chloroform), moderately soluble in cold ethyl acetate, chloroform, or acetone, sparingly soluble in cold alcohol, benzene, ether, and boiling light petroleum, and insoluble in water [Found: C, 75·8; H, 8·6; *M* (Rast), 361·3. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%; *M*, 316·4]. The 2:4-*dinitrophenylhydrazone* formed orange-yellow needles, m. p. 236° (decomp.), from alcohol (Found: C, 62·8; H, 6·0; N, 11·7. $C_{26}H_{32}O_6N_4$ requires C, 62·9; H, 6·5; N, 11·3%). Prepared by the pyridine method at room temperature or by the sodium acetate method in boiling alcohol for 2 hours, the *oxime* separated from alcohol in colourless elongated prisms, m. p. 212°, which on admixture with original compound had m. p. 165—185° (Found: N, 4·4. $C_{20}H_{29}O_3N$ requires N, 4·2%).

Rosonolactone.—The residues from the solutions left on the separation of the crude rosenonolactone fraction, consisting mainly of waxy and fatty material, were triturated with methanol which dissolves the fat and waxy product, leaving *rosonolactone* together with small amounts of rosenonolactone. This residue was extracted with boiling methanol or 90% alcohol, and the extract filtered from a little undissolved rosenonolactone. The solid which was obtained by evaporation of the filtrate was repeatedly treated in the same manner until all the rosenonolactone had been removed. Finally, rosonolactone was crystallised from 90% alcohol or from light petroleum, forming colourless rod-like prisms, m. p. 186°, $[\alpha]_D^{20°}$ −3·0° (*c*, 1 in chloroform) (Found: C, 75·8, 75·7, 75·9; H, 9·3, 9·5, 9·6. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). This compound is considerably more soluble in the usual organic solvents than rosenonolactone. On being boiled with aqueous-alcoholic sodium hydroxide the lactone dissolves, and on evaporation of the alcohol and dilution of the residue with water a clear solution is obtained which only deposits the lactone after having been acidified with hydrochloric acid.

Dihydrorosenonolactone.—Hydrogenation of rosenonolactone (5 g.), dissolved in ethyl acetate (800 ml.), with hydrogen at atmospheric pressure and a palladium–charcoal catalyst (from 1·5 g. of charcoal and 0·15 g. of palladium chloride) was complete in 30—40 minutes. Evaporation of the filtered solution gave the *dihydro*-compound (4·9 g.), m. p. 181—182°, which on recrystallisation from alcohol formed elongated prisms, rather more soluble than the parent substance in the usual organic solvents, m. p. 183°, $[\alpha]_D^{20°}$ −106·0° (*c*, 1 in chloroform) (Found: C, 75·4; H, 9·3. $C_{20}H_{32}O_3$ requires C, 75·4; H, 9·5%). Estimation of *C*-methyl gave 11·4%, whereas $C_{18}H_{24}O_3Me_2$ requires 9·4% and $C_{17}H_{21}O_3Me_3$ requires 14·1%. The *oxime* separated from dilute alcohol in colourless needles, m. p. 250° (decomp.) (Found: N, 4·5. $C_{20}H_{31}O_3N$ requires N, 4·2%), and the semicarbazone from the same solvent in colourless prisms, m. p. 205—207°. The 2:4-*dinitrophenylhydrazone* formed tiny yellow needles, m. p. 250° (decomp.), from alcohol–benzene (Found: N, 11·7. $C_{26}H_{34}O_6N_4$ requires N, 11·3%).

Action of Alcoholic Sodium Hydroxide on Rosenonolactone.—When the lactone (5 g.) was boiled with 5% alcoholic sodium hydroxide (50 ml.) for ½ hour, and the solution cooled and acidified with dilute hydrochloric acid, *iso*rosenonolactone was obtained in colourless, rod-like prisms (4·9 g.), m. p. 140—142°, which on recrystallisation from dilute alcohol had m. p. 144°, $[\alpha]_D^{20°}$ +20·0° (*c*, 1·5 in chloroform) [Found: C, 75·9; H, 8·8; *M* (Rast), 325. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%; *M*, 316·4]. When the hydrolysis is conducted with a measured excess of alcoholic alkali and the excess titrated with phenolphthalein as an indicator, after the completion of the reaction the results indicated that 1 equiv. of sodium hydroxide is required in the formation of the sodium salt of the acid.

For the preparation of the methyl ester of the acid from *iso*rosenonolactone, the compound (1 g.) was heated under reflux with 0·5N-alcoholic sodium hydroxide (7 ml.) for ½ hour, the alcohol was distilled off, the residue was treated with water (150 ml.), the cooled solution was filtered to remove traces of unchanged *iso*rosenonolactone, and the liquor treated drop-wise with silver nitrate solution (0·7 g. in 5 ml. of water). The resulting insoluble silver salt was collected, washed with methanol, and boiled with acetone

(100 ml.) and methyl iodide (2 ml.) for 1 hour. Evaporation of the filtered solution and treatment of the residue with water precipitated the *methyl* ester, which formed colourless needles, m. p. 157—158°, from dilute methanol [Found: C, 72·2, H, 9·7; OMe, 7·0 $C_{20}H_{29}O_3(OMe)$ requires C, 72·4; H, 9·3; OMe, 9·0%].

Interaction of *iso*rosenonolactone with excess of hydroxylamine hydrochloride and pyridine at room temperature for 3 days gave the *oxime*, which separated from aqueous alcohol in elongated colourless prisms, m. p. 180—181° (Found: N, 4·5. $C_{20}H_{29}O_3N$ requires N, 4·2%). The 2 : 4-*dinitrophenylhydrazone* formed yellow elongated prisms, m. p. 231° (decomp.), from 90% alcohol (Found: N, 11·8. $C_{26}H_{32}O_6N_4$ requires N, 11·3%).

Interaction of *iso*rosenonolactone (0·4 g.), acetic anhydride (2 ml.), and pyridine (2 ml.) at room temperature during 4 days gave an *acetyl* derivative (0·4 g.), forming colourless needles, m. p. 183°, from dilute alcohol, $[\alpha]_D^{20°}$ −47·0° (*c*, 1 in chloroform) (Found: C, 73·7; H, 8·4; CH_3·CO, 12·9. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4; CH_3·CO, 12·0%). Interaction of this compound in alcohol with a warm dilute sulphuric acid solution of 2 : 4-dinitrophenylhydrazine sulphate gave rise to the 2 : 4-dinitrophenylhydrazone of *iso*rosenonolactone, m. p. 231° (decomp.) after purification.

Action of Alcoholic Hydrochloric Acid on Rosenono- and iso*Rosenono-lactone.*—A solution of rosenonolactone (0·5 g.) in N-alcoholic hydrochloric acid (50 ml., prepared by diluting concentrated acid with alcohol) was heated on the steam-bath for 2 hours, and on being basified with 2N-aqueous sodium hydroxide the cooled reaction mixture deposited crystalline material. This product was fractionally crystallised from alcohol, giving three main crops: (1) slightly impure rosenonolactone, m. p. 205—206°; (2) allo*rosenonolactone* (A), which formed prisms (0·1 g.), m. p. 216°, after repeated recrystallisation from alcohol and on admixture with rosenonolactone had m. p. 204—206° [Found: C, 75·9; H, 8·8; *M* (Rast), 316·3. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%; *M*, 316·4]; (3) *iso*rosenonolactone, m. p. and mixed m. p. 144°, from the alcoholic residues left after the separation of the crude *allo*rosenonolactone.

Acidification of the aqueous liquor left on filtration of the crystalline product with carbon dioxide gave a solid (B) in needles (50 mg.), m. p. 180—190°, which on recrystallisation from benzene or aqueous acetone had m. p. 210° and was soluble in dilute aqueous sodium hydroxide or carbonate but not in aqueous sodium hydrogen carbonate (Found: C, 75·8; H, 8·7. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%).

Under the same conditions *iso*rosenono- gave *allo*rosenonolactone, m. p. and mixed m. p. 216°, and (B), m. p. and mixed m. p. 210° after purification, along with unchanged *iso*rosenonolactone.

Ozonolysis of Rosenonolactone.—A slow stream of ozone and oxygen was passed into a solution of the lactone (0·5 g.) in anhydrous chloroform (50 ml.) for 1 hour, and the solution evaporated in a vacuum. The combined residual products from two experiments were treated with water (200 ml.), and next day the mixture was heated on the steam-bath for 45 minutes, part of the aqueous liquor was distilled off, and the distillate (50 ml.) treated with an aqueous solution of 2 : 4-dinitrophenylhydrazine sulphate, giving a precipitate of formaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 163—164°, identical with an authentic specimen. The residual aqueous liquor in the distilling flask was repeatedly extracted with ether, and the combined extracts washed with dilute aqueous sodium hydroxide. Acidification of the alkaline washings gave an *acid*, which separated from alcohol or aqueous acetone in colourless needles (0·15 g.), m. p. 260° (decomp.) [Found: C, 68·4; H, 7·9; *M* (by titration), 310. $C_{19}H_{26}O_5$ requires C, 68·3; H, 7·8%; *M*, 334]. The oxime of this acid formed prisms, m. p. 256—257°, from dilute alcohol. Mixed with the parent substance this derivative melted at 230—240°.

*Dihydro*iso*rosenonolactone.*—Treatment of dihydrorosenonolactone with warm dilute alcoholic sodium hydroxide, according to the procedure employed for converting rosenono- into *iso*rosenono-lactone, gave rise to *dihydro*iso*rosenonolactone*, which formed colourless rod-like prisms, m. p. 150°, $[\alpha]_D^{20°}$ +34·0° (*c*, 1 in chloroform), from dilute alcohol, easily soluble in alcohol (Found: C, 75·4; H, 9·4. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The 2 : 4-dinitrophenylhydrazone formed tiny elongated prisms, m. p. 250° and mixed m. p. 250° (decomp.), identical with the derivative from dihydrorosenonolactone (Found: N, 11·7%). Acetylation of the lactone with acetic anhydride–pyridine at room temperature for 4 days gave the *acetyl* derivative, which separated from alcohol in colourless elongated prisms, m. p. 184°, $[\alpha]_D^{20°}$ −34·0° (*c*, 1 in chloroform) [Found: C, 73·6; H, 8·9; CH_3·CO, 12·7. $C_{20}H_{29}O_3(CO{\cdot}CH_3)$ requires C, 73·3; H, 9·0; CH_3·CO, 12·0%]. Prepared by way of the sodium salt and the silver salt, the *methyl* ester of dihydro*iso*rosenonic acid formed colourless shining plates, m. p. 165°, from dilute methanol [Found: C, 72·1; H, 9·3; OMe, 6·7. $C_{20}H_{31}O_3(OMe)$ requires C, 72·0; H, 9·7; OMe, 8·9%]. Hydrogenation of *iso*rosenonolactone (2 g.), dissolved in alcohol (250 ml.), with hydrogen at atmospheric pressure and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·1 g. of palladium chloride) was complete in about 30 minutes and on isolation the *dihydro*-derivative (1·9 g.), m. p. 147°, separated from dilute alcohol in colourless needles, m. p. 150°, identical with a specimen prepared by the action of alkali on dihydrorosenonolactone (Found: C, 75·3; H, 9·2%). The acetyl derivative had m. p. and mixed m. p. 184°.

*Oxidation of Dihydro*iso*rosenonolactone.*—Hydrogenation of rosenonolactone (10 g.) gave the dihydrolactone (9·8 g.), which was heated under reflux with 0·5N-alcoholic sodium hydroxide (83 ml., *i.e.*, 8·5 ml. per g.) for ½ hour. After having been diluted with water, the alcohol was removed completely by distillation in a vacuum, and the volume of the residue made up to one litre with water. Next day the solution was filtered to remove a small amount of unchanged material and divided into two equal portions. Each portion was shaken and treated with a mixture of equal parts of powdered potassium permanganate and anhydrous sodium carbonate added in portions of 0·1—0·2 g. At first the permanganate was taken up rapidly, but after 3—4 hours, when 2·8 g. of permanganate had been added, the oxidation proceeded much more slowly. At this stage the combined solutions were decolourised with the minimum amount of sulphur dioxide, acidified with hydrochloric acid, and kept for 24 hours. The white crystalline precipitate was collected and extracted with a little aqueous sodium carbonate, leaving unchanged dihydro*iso*rosenonolactone (4·22 g.), and on acidification the alkaline extract gave acidic material (4·4 g.). The unchanged dihydro*iso*rosenonolactone was converted into the sodium salt of the acid and oxidised with proportionate amounts of potassium permanganate. Eventually a combined yield of 6·28 g. of acidic product together with 2·05 g. of unchanged lactone was obtained. The acidic fraction, which

contained much gummy impurities, had m. p. 180—200° and, on crystallisation from ethyl acetate and then acetone, formed small colourless needles, m. p. 232°, $[\alpha]_D^{20°}$ +4·0° (*c*, 1 in chloroform) (Found: C, 68·3; H, 8·5; *M* (by titration), 386. $C_{20}H_{30}O_5$ requires C, 68·6; H, 8·6%; *M*, 350·4). This compound, which is only slightly soluble in hot water and readily soluble in aqueous sodium hydrogen carbonate, does not appear to react readily with semicarbazide acetate or with 2 : 4-dinitrophenylhydrazine. On treatment with ethereal diazomethane the acid gave a *methyl* ester, forming prisms, m. p. 97—98° [Found: OMe, 8·5. $C_{20}H_{29}O_4(OMe)$ requires OMe, 8·5%], from dilute methanol. Attempted acetylation by the pyridine method at room temperature gave an *anhydro*-derivative which was acidic, being readily soluble in aqueous sodium hydrogen carbonate, and formed colourless blunt needles, m. p. 212°, from dilute acetone (Found: C, 72·6; H, 8·5. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%). Unlike the parent acid, this compound does not appear readily to form the cyclic ketone responsible for the menthone-like odour.

A solution of the acid (1 g.), m. p. 232°, in 0·5N-aqueous sodium hydroxide (40 ml.) was kept at room temperature for 3 days; after a few hours the pale yellow liquid developed the characteristic odour, and oily globules began to separate. The solution was diluted somewhat, and the volatile ketonic product removed by a current of steam and then isolated from the distillate with ether. The aqueous residual hydrolysate was acidified with dilute hydrochloric acid and extracted three times with ether. Evaporation of the combined extracts left a small amount of acid which has not yet been investigated. The acidified aqueous liquors were then repeatedly extracted with ethyl acetate, and on evaporation of the dried extracts a pale yellow crystalline *acid* (0·35—0·4 g.), m. p. 199—200°, was obtained. Recrystallised from ethyl acetate, this compound formed large colourless polyhedra, m. p. 205° after softening at 195°, $[\alpha]_D^{20°}$ −28·0° (*c*, 1 in water), insoluble in cold ether, benzene, or chloroform, sparingly soluble in cold ethyl acetate or acetone, and moderately soluble in water or dioxan (Found: C, 56·1; H, 6·4. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The equivalent weight of this compound as determined by titration with alkali was 87·6, but by potentiometric titration the value was 110, whereas the theoretical equivalent for two carboxyl groups is 107. In the latter titration only one inflexion point was obtained on the curve. The 2 : 4-dinitrophenylhydrazone formed yellow needles, m. p. 205—206°, from benzene–alcohol. Esterification of this acid with ethereal diazomethane yielded a liquid dimethyl ester which gave rise to a *semicarbazone*, forming elongated prisms, m. p. 217—218°, from benzene–methanol [Found: OMe, 19·7; N, 13·6. $C_{11}H_{15}O_5N_3(OMe)_2$ requires OMe, 20·7; N, 14·0%].

The Ketone $C_{10}H_{18}O$.—This compound was isolated from the foregoing oxidation product as a colourless oil (0·35 g.) which readily yielded ketonic derivatives but did not decolourise neutral potassium permanganate in acetone. The crude ketone (1·07 g.) was readily oximated with excess of hydroxylamine hydrochloride and sodium acetate, and the *oxime* was separated from the reaction mixture by distillation in a current of steam, crystallising from the distillate in elongated prisms. Recrystallised from dilute methanol, the compound (0·92 g.) had m. p. 56—57° (Found: C, 70·8; H, 11·2; N, 8·1; *C*-Me, 16·7. $C_8H_{13}ONMe_2$ requires C, 71·0; H, 11·3; N, 8·3; *C*-Me, 17·8%). Prepared in the usual way, the *semicarbazone* separated from methanol or alcohol in colourless needles, m. p. 178°, $[\alpha]_D^{20°}$ +17·0° (*c*, 1 in chloroform) (Found: C, 62·3; H, 9·7; N, 20·0. $C_{11}H_{21}ON_3$ requires C, 62·6; H, 10·0; N, 19·9%).

Thionyl chloride (0·5 ml.) in ether (5 ml.) was added drop-wise to a solution of the oxime (0·48 g.) in ether (20 ml.) kept at about −5° during 10 minutes. The white precipitate which first separated became slightly gummy. After having been kept for a further 10 minutes, the reaction mixture was treated with water (25 ml.) and extracted with ether. Evaporation of the dried extracts left an oil which rapidly solidified, m. p. 50—52°, and on recrystallisation from light petroleum (b. p. 40—45°) and then water, this *compound* formed colourless needles, m. p. 55°, which on admixture with the oxime melted at room temperature (Found: C, 64·4; H, 11·4; N, 7·5. $C_{10}H_{19}ON,H_2O$ requires C, 64·2; H, 11·2; N, 7·5%. Calc. for $C_{10}H_{19}ON$: C, 71·0; H, 11·2; N, 8·3%). The substance is volatile in steam, and on being dried in a vacuum desiccator melts and then resolidifies on exposure to the moist atmosphere.

On being heated, a mixture of the ketone (1·2 g.), selenium dioxide (1·2 g.), and acetic anhydride (1·5 ml.) began to boil at 130° (oil-bath) and 5 minutes later the temperature was raised to 140°. After having been kept at 140° for 35 minutes, the cooled mixture was filtered, almost neutralised with sodium carbonate, and extracted with ether. Repeated extraction of the ethereal solution with aqueous sodium hydroxide followed by acidification of the combined alkaline extracts and then the removal of traces of volatile matter by a current of steam left a non-volatile residue which was isolated with ether and triturated with dilute hydrogen peroxide. Crystallised from benzene–light petroleum (b. p. 60—80°), the *acid* formed colourless prisms, m. p. 145—146°, insoluble in water but readily soluble in aqueous sodium hydrogen carbonate (Found: C, 59·8; H, 8·8. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

A slow stream of ozone and oxygen, saturated with carbon tetrachloride vapour at room temperature, was passed into a solution of the ketone $C_{10}H_{18}O$ (0·9 g.) in carbon tetrachloride (5 ml.) at room temperature for 20 hours. The solution was diluted with ether and extracted with aqueous sodium carbonate. From the ether a mixture (0·52 g.) of unchanged ketone and another product was obtained, and acidification of the aqueous sodium carbonate extracts gave a liquid keto-acid (0·36 g.), which was isolated with ether and purified by distillation in a vacuum, giving two fractions: (*a*) (30 mg.), b. p. 80—100°/23 mm., and (*b*) (200 mg.), b. p. 180—210°/23 mm. The latter fraction, which gave the reactions of a ketonic acid and an iodoform reaction, was converted into the *semicarbazone* (0·08 g. from 0·11 g. of acid), which formed prisms, m. p. 166°, $[\alpha]_D^{22°}$ +12·0° (*c*, 0·5 in alcohol), from dilute alcohol (Found: C, 54·4; H, 8·7; N, 17·2. $C_{11}H_{21}O_3N_3$ requires C, 54·3; H, 8·6; N, 17·3%).

UNIVERSITY OF LIVERPOOL. [*Received, July 29th*, 1948.]

186. *The Chemistry of Bacteria. Part II. Some Degradation Products of Violacein.*

By R. J. S. Beer, Kenneth Clarke, H. G. Khorana, and Alexander Robertson.

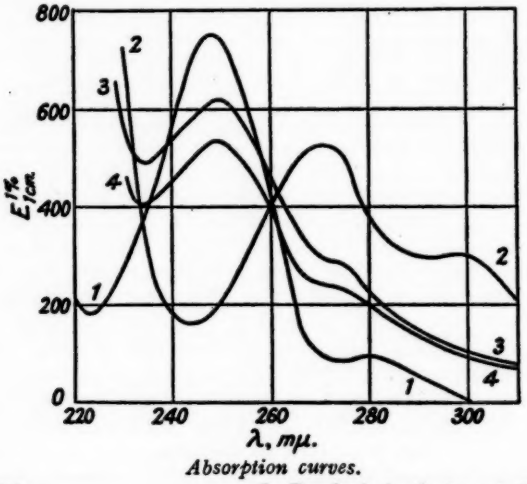
Thermal decomposition of violacein, from *Chromobacterium violaceum*, gives a mixture in small yield from which oxindole and 5-hydroxyindole, as its picrate, have been isolated. In agreement with this result it has been found that oxidation of the acetyl derivative of violacein gives a neutral fraction and a mixture of at least three acids from which *N*-acetylanthranilic acid and 2-acetamido-5-acetoxybenzoic acid have been isolated. From the neutral fraction of the oxidation product isatin has been separated. On the basis of these findings the violacein molecule is considered to contain an indole and a hydroxyindole residue.

The intensely violet phenolic pigment violacein produced by *Chromobacterium violaceum* has been isolated in the amorphous form by a number of workers, *e.g.*, Hartley (*Sci. Proc. Roy. Dublin Soc.*, 1913, **14**, 63), Lasseur and Girardet (*Bull. Trimistriel. Soc. Sci., Nancy*, 1926, **3**, 1), Reilly and Pyne (*Biochem. J.*, 1927, **21**, 1059), and Tobie (*J. Bact.*, 1935, **29**, 223), who have studied the properties of the substance. As might be expected the results obtained with amorphous material have been inconclusive, and further, the colouring matters described by Sartory *et al.* (*Compt. rend.*, 1938, **206**, 950; *Bull. Sci. Pharm.*, 1938, **45**, 302) and by Friedheim (*Compt. rend. Soc. Biol.*, 1932, **110**, 352; *Arch. Sci. phys. nat.*, 1932, **14**, 125) appear to differ so considerably from violacein that it is doubtful if they are the same pigment. Crystalline violacein appears to have been first obtained by Kögl and Tönnis (unpublished work; see "Handbuch der Pflanzenanalyse", 1932, Vol. III, Part 2, p. 1443) who like some of the earlier workers cultivated the organism in a liquid medium. Essentially the same procedure has been described by Strong (*Science*, 1944, **100**, 287), but the amount of the colouring matter obtained in this way is small, about 710 mg. from 65 l. of medium. In the course of an investigation of the chemistry and constitution of this pigment in these laboratories some improvement in the yield has been effected by the use of a solid medium, but the quantity available for investigation is limited and as it is hoped to improve still further the method of culture, full details will be published when the experiments directed to this end have been completed.

Comparatively little is known regarding the chemical nature of violacein, and the empirical formulæ proposed by Reilly and Pyne (*loc. cit.*) and by Tobie (*Proc. Soc. Exp. Biol. Med.*, 1936, **34**, 620), derived from analyses of the amorphous pigment, may be neglected. On the basis of their analytical results obtained with crystalline material, Kögl and Tönnis (*loc. cit.*) suggested the empirical formula $C_{35}H_{25}O_6N_5$ or $C_{42}H_{30}O_7N_6$ for violacein, whilst the analyses obtained by Wrede (*Z. physiol. Chem.*, 1934, **223**, 113; *Arch. exp. Path. Pharm.*, 1937, **186**, 532), who showed that the pigment formed comparatively stable crystalline addition compounds with a number of bases—aniline, chloroaniline, pyridine, and chloropyridine—point to the empirical formula $C_{42}H_{28}O_7N_6$ rather than $C_{35}H_{23}O_6N_5$. The analytical figures for specimens of violacein and its acetyl derivative prepared in this laboratory (unpublished work) are in agreement with those of Wrede (*loc. cit.*), but a decision regarding the empirical formula cannot be made profitably at this stage, more especially since the extremely low solubility of the compound in suitable solvents precludes accurate molecular-weight determinations. With violacein the results of nitrogen estimations are unexpectedly variable (cf. Wrede, *loc. cit.*). Whilst Kögl and Tönnis (*loc. cit.*) and Wrede (*loc. cit.*) have described the general properties of the crystalline compound and its acetate, no identifiable major degradation products have hitherto been reported other than the formation of traces of oils (pyrrolic ?) by distillation with zinc dust and other violent degradations reported by Wrede and by Tobie (*loc. cit.*), who also claimed to have obtained an indication of the presence of anthranilic acid by a colour reaction in a solution resulting from a hydrolytic process (*J. Bact.*, 1938, **35**, 11).

In 1938, Dr. T. S. Subramanian, working in this laboratory, observed that when violacein was heated with zinc dust in a vacuum a white sublimate was produced in small amount from which material, m. p. 112°, was separated. This product gave a strong Ehrlich reaction and had the composition C_8H_7ON. On reinvestigating this reaction we have found that when heated in a vacuum or in a slow stream of nitrogen, alone or mixed with zinc dust or copper powder, violacein decomposes vigorously, and a poor yield of a volatile crystalline product is obtained, the main component of which is oxindole (I). Oxindole was isolated by fractional crystallisation of the pyrolysis product, and in addition there was obtained a fraction, m. p. 102—103°, which had the composition and some of the properties of a hydroxyindole but did not appear to be identical with any of the isomeric synthetic hydroxyindoles (Part I, *J.*, 1948, 1605). Examination

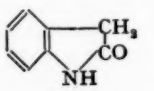
of the ultra-violet spectrum of this product indicated that, in all probability, it contained a considerable proportion of oxindole mixed with the compound responsible for the Ehrlich reaction, presumably a hydroxyindole. Though owing to lack of material it has not been possible to resolve this mixture, we have isolated from it a small amount of an orange-red picrate which corresponds in every respect with a sample of the picrate of authentic 5-hydroxyindole (II). Further, it has been observed that crystallisation of a mixture of 5-hydroxyindole (1 part) and oxindole (2 parts) gives rise to a product, m. p. 101—103°. This is not regarded as a



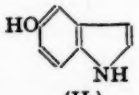
Absorption curves.

1. *Oxindole.*
2. *5-Hydroxyindole.*
3. *Pyrolysis product, m. p.* 102—103°.
4. *Mixture of* 1 *and* 2, *m. p.* 103—104°.

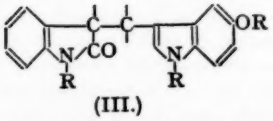
genuine addition compound containing stoicheiometric amounts of the components because the melting point was slightly raised (to 103—104°) by recrystallisation. The absorption curve of the artificial mixture of oxindole and 5-hydroxyindole, m. p. 103—104°, cuts the curve for oxindole at the expected isobestic points. That of the pyrolysis product, m. p. 102—103°, is qualitatively very similar to the curve for the artificial mixture, but the absorption is slightly more intense, suggesting the presence of a third product with continuous end absorption rising gradually from 300 mμ to 230 mμ. When the pyrolysis product was treated directly with picric acid in benzene there was obtained a trace of a second deep red crystalline picrate, and this observation, in conjunction with the unpleasantly characteristic smell of the crude material (the hydroxyindoles are odourless), suggests that small amounts of at least one other indole are present (cf. Wrede, *loc. cit.*).



(I.)



(II.)



(III.)

Oxidative degradation of violacein has not so far yielded any identifiable product, probably because the phenolic system renders the molecule too sensitive, and on this account we have turned to a study of the degradation of acetylviolacein. From the mixture formed when the oxidation was effected with chromic oxide in hot acetic acid, a mixture of acidic substances was isolated from which *N*-acetylanthranilic acid was separated in comparatively large amount. On repeating the oxidation at room temperature a somewhat higher yield of a similar acidic mixture was obtained, of which the main component was again *N*-acetylanthranilic acid. A second acid was isolated but could not be obtained in an absolutely pure state. Esterification of this substance with diazomethane and subsequent distillation of the product in a high vacuum ultimately gave a pure specimen of the methyl ester, obtained in two crystalline forms, m. p. 103—104° and 106—107°, which from its analytical results appeared to be the diacetyl derivative of a methyl hydroxyanthranilate. From the colour reactions given by a solution of the deacetylated acid it appeared probable that the parent oxidation product was *2-acetamido-5-acetoxybenzoic acid*. Accordingly *methyl 2-acetamido-5-acetoxybenzoate* was synthesised and found to be identical with

the methyl ester of the degradation product. From the aqueous liquors left after the separation of the main acidic oxidation products there was isolated by continuous ethereal extraction a mixture which, in addition to a small quantity of mixed acids, contained isatin.

It seems probable, from the production of *N*-acetylanthranilic acid and isatin by oxidation of acetylviolacein and of oxindole by thermal decomposition of the parent pigment, that the violacein molecule contains an oxindole nucleus or one closely related to it, the nitrogen atom of which bears an acetyl group in acetylviolacein. There is, however, no direct evidence as yet that these degradation products have their origin in the same part of the molecule. Similarly, it is a reasonable hypothesis that the diacetyl derivative of 5-hydroxyanthranilic acid arises from a 5-acetoxy-1-acetylindole residue in acetylviolacein, and that it is this part of the molecule which affords 5-hydroxyindole in the pyrolysis of violacein itself, although it is, of course, conceivable that this product arises as the result of a rearrangement. The expression (III; R = H) represents one of the possible ways in which the two indole nuclei may be linked in the pigment. The acetyl derivative would then be (III; R = Ac).

In the course of earlier attempts to define the nature of the mixture, m. p. 112°, from the pyrolysis of violacein, this material was compared with the hydroxytolyl cyanides which have the same composition, although it seemed unlikely that the latter compounds would give a positive Ehrlich reaction. Of the ten possible members of this series five were known, and the preparation of the other five, *i.e.*, 3-*hydroxy*-, 4-*hydroxy*-, and 5-*hydroxy*-o-*tolyl cyanide*, 5-*hydroxy*-m-*tolyl cyanide*, and 3-*hydroxy*-p-*tolyl cyanide*, by standard procedures is described in the experimental section.

Experimental.

Pyrolysis of Violacein.—An intimate mixture of crystalline violacein (100 mg.) and zinc dust (1·0 g.) was heated in a small retort in a vacuum at 330°/0·1 mm. for 1½ hours, and a colourless product distilled on to the cooler part of the retort tube where the liquid solidified. The distillate (80—100 mg.) from 10 experiments was combined and fractionally crystallised from light petroleum (b. p. 60—80°), and the following two apparently homogeneous substances were isolated :

(*a*) A compound forming long needles (20 mg.), m. p. 126°, from light petroleum (b. p. 60—80°), undepressed on admixture with an authentic specimen of oxindole, m. p. 126—127°, with which its properties were identical [Found : C, 72·0; H, 5·8; N, 10·6; *M* (Rast), 139·1. Calc. for C_8H_7ON : C, 72·2; H, 5·3; N, 10·5%; *M*, 133]. The ultra-violet absorption spectrum of the specimen dissolved in alcohol shows $\lambda_{max.}$ 248·5 mμ, $\varepsilon_{max.}$ 9930, with a weak maximum at 280 mμ, ε 1260. This agrees well with the absorption curve recorded by Ramart-Lucas and Biquard (*Bull. Soc. chim.*, 1935, **2**, 1387).

(*b*) A product obtained in very faintly yellow flakes (22 mg.), m. p. 102—103°, soluble in dilute aqueous sodium hydroxide and giving a greenish-yellow colouration, ultimately changing to brown, with aqueous ferric chloride (Found : C, 71·9, 71·9; H, 5·1, 5·7; N, 10·5. Calc. for C_8H_7ON : C, 72·2; H, 5·3; N, 10·5%). This material gave an intense red colouration, tinged with blue, with Ehrlich's reagent and a positive nitroprusside test for indoles. In spite of the close similarity to the hydroxyindoles (Part I, *loc. cit.*), a mixture of this material with either 4-hydroxy- (m. p. 98°), 5-hydroxy- (m. p. 107°), or 7-hydroxy-indole (m. p. 96°) showed a depression in m. p., and the ultra-violet absorption spectrum (see figure) was markedly different from those of the synthetic hydroxyindoles, and suggested that a high proportion of oxindole was present together with a much smaller amount of one or other of the isomeric hydroxyindoles.

When picric acid (27 mg.), dissolved in the minimum amount of warm benzene, was added to a solution of the material (17 mg.), m. p. 102—103°, in a small volume of the same solvent, a crystalline picrate began to separate almost immediately. On isolation, the compound (7 mg.) had m. p. 162° (decomp.) and was recrystallised with little loss from benzene mixed with a trace of light petroleum, forming clusters of elongated orange-red needles, m. p. 166—167° (decomp.) (bath preheated to 100°) after slight shrinking and darkening. This derivative corresponds in colour, crystal form, and habit with the authentic picrate of 5-hydroxyindole, m. p. 167° (decomp.), and a mixture of the two picrates had the same m. p. Both derivatives have a somewhat lighter colour than the picrates of the other hydroxyindoles which have been prepared (Part I, *loc. cit.*). The same mixture of products was obtained when zinc dust was replaced by copper powder and when the reaction was carried out in a slow stream of nitrogen at atmospheric pressure. Modification of the conditions in a variety of ways failed to increase the proportion of 5-hydroxyindole in the crude pyrolysis product.

Oxidation of Acetylviolacein with Chromium Trioxide.—(*A*) To boiling acetic acid (35 ml.) containing acetylviolacein (Wrede, *loc. cit.*) (200 mg.) in suspension a warm solution of chromic acid in acetic acid (approximately 3·5 ml. of a 10% solution) was gradually added until the original deep red colour changed to a clear green (5—10 minutes). After having been kept at room temperature for one hour the mixture was diluted with water (110 ml.) and extracted several times with ether. By this means a brown tar was isolated which was separated into benzene-soluble and benzene-insoluble fractions. The latter fraction was triturated with aqueous sodium hydrogen carbonate, the extract filtered to remove non-acidic resinous material, the filtrate acidified and exhaustively extracted with ether, and the combined dried extracts evaporated, leaving a small amount of an acidic product. Crystallised by slow evaporation of an ethyl acetate–light petroleum (b. p. 60—80°) solution, the material from five oxidation experiments gave an acid in short yellow needles, m. p. 214—218°, which was not further purified owing to lack of material but was converted into the methyl ester by means of diazomethane. This compound could be readily crystallised from benzene, forming colourless needles, m. p. 163° (Found : C, 55·9; H, 4·6; N, 6·5. Calc. for $C_{11}H_{11}O_4N$: C, 55·7; H, 4·7; N, 5·9%).

The benzene-soluble fraction from five experiments, dissolved in a little benzene, was treated with a little light petroleum (b. p. 60—80°), giving a pale yellow precipitate (*ca.* 70 mg.) from which two acids were separated by fractional crystallisation from light petroleum (b. p. 80—100°). After repeated purification from benzene the more soluble acid was obtained in colourless needles, m. p. 181°, and identified by comparison with an authentic specimen of *N*-acetylanthranilic acid, m. p. 185°; a mixture of the two specimens melted at 183—184° (Found : C, 60·6; H, 5·3; N, 7·5. Calc. for $C_9H_9O_3N$: C, 60·3; H, 5·0; N, 7·8%). Prepared by means of diazomethane, the methyl ester formed shining needles, m. p. 100°, undepressed on admixture with an authentic specimen, m. p. 100—101°.

The second acid isolated from the benzene soluble fraction was obtained in larger amount by method (*B*) and is described below.

(*B*) Acetylviolacein (1 g.) suspended in acetic acid (250 ml.) was treated with a 5% solution of chromium trioxide in acetic acid (27 ml.), and the mixture kept for 20—24 hours with occasional shaking and filtered to remove a little unchanged pigment. The green concentrate (*ca.* 25 ml.) left on evaporation of the filtrate under reduced pressure was treated with water (250 ml.) and repeatedly extracted with ether, giving extract (*X*). The residual aqueous solution was then further exhausted with ether in a continuous extraction apparatus, giving extract (*Y*).

Evaporation of the extract (*X*) left a reddish-brown gum which was thoroughly triturated with 2N-sodium hydrogen carbonate (30 ml.), leaving a dark viscous undissolved residue (30—35 mg.). The filtered hydrogen carbonate solution was acidified and repeatedly extracted with ether (the residual aqueous liquor was finally combined with the liquor in the continuous extractor). Evaporation of the dried extracts left a gum which was digested with successive small portions of boiling light petroleum (b. p. 80—100°), the later portions of solvent containing an increasing proportion of benzene. In this manner four main fractions were obtained from the gum : (*a*) extracted with light petroleum, (*b*) with light petroleum containing 25% benzene, (*c*) with equal parts of light petroleum and benzene, and (*d*) a benzene-insoluble residue. On cooling, each extract deposited colourless crystalline material, and as the crops from (*a*) and (*b*) were found to be similar they were combined and designated substance (M_1) (130 mg. and 15 mg. obtained by concentration of the mother liquor); (*c*) gave (M_2) and (*d*) the residue (M_3).

The material M_1, m. p. *ca.* 135—140°, was found to contain *N*-acetylanthranilic acid and a smaller amount of a second acid. As the separation of the components by crystallisation proved difficult, the mixture was esterified with diazomethane and the mixed methyl esters (200 mg.) distilled in a high vacuum at 0·02 mm., giving 3 fractions. The first fraction, obtained with the bath at 110—120°, consisted of colourless crystals (110 mg.), m. p. 94—96°, which on recrystallisation from light petroleum (b. p. 60—80°) had m. p. 98—100°, undepressed on admixture with authentic methyl *N*-acetylanthranilate. The second fraction, which distilled with bath temperature about 140°, formed colourless crystals (47 mg.), m. p. *ca.* 89°, with previous sintering, and then m. p. 100—101° after recrystallisation from light petroleum (yield, 30 mg.). The third fraction, bath temperature 140—160°, was obtained in colourless crystals (23 mg.), m. p. 98—100°, and on recrystallisation from light petroleum gave a substance, m. p. 104—106°. The recrystallised products from the second and third fractions consisted mainly of the methyl ester of M_2 with which they were ultimately identified.

The product M_2 had m. p. about 176° after sintering at about 165°, and on recrystallisation formed an apparently homogeneous mass of colourless flakes which on being heated in a capillary tube shrank slightly at 150°, softened at 165°, and melted at 175—182°. This behaviour was not materially affected by numerous crystallisations from benzene or toluene, and, presumably owing to loss of solvent of crystallisation, the originally clear crystals became opaque on being kept at room temperature. When a little of the parent acid was deacetylated by being heated with a little N-hydrochloric acid, the solution gave a positive test for a primary amine (diazotisation), and the basified solution had a strong blue fluorescence. Prepared by means of ethereal diazomethane, the *methyl* ester formed clusters of colourless needles, m. p. *ca.* 100°, from light petroleum (b. p. 60—80°), and was then purified by distillation in a vacuum, bath temperature 150—160°/0·05 mm. On recrystallisation from light petroleum (b. p. 60—80°) the distillate gave methyl 2-acetamido-5-acetoxybenzoate in flat needles or plates, m. p. 106—107°, undepressed on admixture with a synthetic specimen [Found in specimen dried in a high vacuum at 40° : C, 57·3; H, 5·1; N, 5·6; OMe, 11·3; Ac, 42·0. $C_7H_4O_2N(OMe)Ac_2$, requires C, 57·4; H, 5·2; N, 5·6; OMe, 12·4; Ac, 34·2%].

The benzene-insoluble residue M_3, collected from a number of oxidations, was extracted with aqueous sodium hydrogen carbonate, giving on acidification of the extract a small amount of an acid which separated from methanol–benzene in faintly coloured rectangular prisms, m. p. 230—231° (decomp.) after sintering about 227°. After having been sublimed at 160°/0·02 mm. this acid had m. p. 235—236° (decomp.). With ethereal diazomethane the partially purified acid gave a methyl ester which formed almost colourless needles, m. p. 150—165°, and was then separated from traces of a more volatile ester by sublimation at 140—145°/0·02 mm., being obtained as a colourless crystalline compound, m. p. 165—166° after sintering at 158°.

The extract (*Y*) (from 3 g. of acetylviolacein) was evaporated under reduced pressure, and a solution of the residue in a little methanol was treated with 2N-sodium hydrogen carbonate (50 ml.). The mixture was repeatedly extracted with ether, giving a non-acidic fraction, and from the aqueous hydrogen carbonate an acidic fraction was isolated after acidification with hydrochloric acid. On being heated in a small sublimation retort at 160—180°/0·001 mm. the non-acidic gum gave an orange-red crystalline sublimate (45 mg.), m. p. 196° after sintering, which on recrystallisation from benzene with little loss of material gave isatin in orange-red prisms, m. p. 199—200°, unchanged on further crystallisation or admixture with an authentic specimen, m. p. 201—202° (Found : C, 65·4; H, 3·4. Calc. for $C_8H_5O_2N$: C, 65·3; H, 3·4%). The acidic fraction was esterified with diazomethane and the ester distilled in a vacuum, giving several different esters in amounts too small to permit further investigation at present.

2-Acetamido-5-acetoxybenzoic Acid.—Acetylation of 5-hydroxyanthranilic acid (Limpricht, *Annalen*, 1892, **263**, 224) (0·2 g.), dissolved in 2% aqueous sodium hydroxide (10 ml.), with acetic anhydride (0·35 g.) at 0° in the course of a few minutes and subsequent addition of a slight excess of hydrochloric acid gave the *diacetyl* derivative (0·3 g.), m. p. 188—189° (Found in material dried in a high vacuum at 80° : C,

56·1; H, 4·6. $C_{11}H_{11}O_5N$ requires C, 55·7; H, 4·6%). Like those of the acid from acetylviolacein, the crystals of the synthetic diacetate became opaque on being kept. Esterification of this acid (0·12 g.) with a slight excess of ethereal diazomethane gave the *methyl* ester, forming from light petroleum (b. p. 60—80°), clusters of colourless needles, m. p. 103—104°, which on sublimation at 150—160°/0·02 mm. and subsequent recrystallisation had the same m. p. 103—104° (Found in material dried in a high vacuum at 40°: C, 57·5; H, 5·2. $C_{13}H_{13}O_5N$ requires C, 57·4; H, 5·2%). This ester was observed to exist in two crystalline forms; *viz.*, the form in needles, m. p. 103—104°, which was usually obtained, and the form in plates or flattened needles, m. p. 106—107°, originally obtained by inoculating a warm solution of the lower-melting form with a natural specimen obtained by the oxidation of violacein. When a mixture of the two forms, which begins to melt at 103°, was kept at this temperature for a few minutes, cooled, and then heated, it melted at 107°, but when a mixture of the two forms was melted completely and allowed to solidify it then had m. p. 102—103°.

A specimen of the ester obtained from violacein behaved in exactly the same manner.

(With D. J. McKeand.)

3-*Hydroxy*-o-*tolyl Cyanide*.—A solution of 3-amino-*o*-tolyl cyanide (Gabriel and Tieme, *Ber.*, 1919, **52**, 1079) (2 g.) in dilute sulphuric acid (20 ml.), kept at 0°, was treated with slightly more than one molecular proportion of aqueous sodium nitrite, the excess of nitrite destroyed with a little urea, and the diazonium sulphate solution added dropwise to boiling sulphuric acid (35 ml. of concentrated acid and 70 ml. of water). After isolation the product was crystallised from benzene–light petroleum (b. p. 60—80°), and the *cyanide* obtained in colourless prisms; m. p. 110—111° (Found: N, 10·7. C_8H_7ON requires N, 10·5%).

4-*Hydroxy*-o-*tolyl Cyanide*.—4-Amino-*o*-tolyl cyanide (Borsche and Wagner-Roemmich, *Annalen*, 1941, **546**, 277) (5 g.) was diazotised in sulphuric acid, and the resulting sulphate converted into 4-*hydroxy*-o-*tolyl cyanide* by the procedure employed for the 3-hydroxy-compound. The product formed colourless needles (1 g.), m. p. 100—101°, from light petroleum (b. p. 60—80°) (Found: C, 72·4; H, 5·4; N, 10·2. C_8H_7ON requires C, 72·2; H, 5·3; N, 10·5%). Acetylation by the pyridine–acetic anhydride method gave the *acetyl* derivative, which crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 63·5—64° (Found: C, 68·6; H, 5·2; N, 7·9. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1; N, 8·0%).

5-*Hydroxy*-o-*tolyl Cyanide*.—The *oxime* of 5-hydroxy-*o*-tolualdehyde (Gattermann, *Annalen*, 1907, **357**, 322) formed needles, m. p. 151—152°, from water (Found: C, 63·9; H, 5·9; N, 9·3. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%). Dehydration of this compound (1 g.) with acetic anhydride gave 5-*acetoxy*-o-*tolyl cyanide* which crystallised from light petroleum (b. p. 60—80°) in prisms (0·7 g.), m. p. 45·5—46·5° (Found: C, 68·6; H, 5·1; N, 7·7%). On deacetylation, this acetate (0·7 g.) furnished the *cyanide* (0·5 g.), which formed prisms, m. p. 135—136°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 72·2; H, 5·5; N, 10·7%).

5-*Hydroxy*-m-*tolyl Cyanide*.—The *acetyl* derivative of 5-hydroxy-*m*-toluic acid (Meldrum and Perkin, *J.*, 1909, **95**, 1896) formed colourless needles, m. p. 107·5—109·5° (Found: C, 61·5; H, 5·2. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%). The acid chloride was prepared from the compound (2 g.) with phosphorus pentachloride (2·1 g.) in chloroform (30 ml.) and converted into the *amide*, which separated from water in needles (1·5 g.), m. p. 139—140° (Found: C, 61·9; H, 5·5; N, 6·8. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3%). Dehydration of the amide (1 g.) with boiling phosphorus oxychloride (0·5 g.) containing sodium chloride (0·5 g.) for 30 minutes gave the acetoxy-cyanide which on deacetylation furnished 5-*hydroxy*-m-*tolyl cyanide* (0·3 g.), which formed needles, m. p. 103·5—104·5°, from benzene–light petroleum (Found: C, 71·9; H, 5·3; N, 10·2%).

3-*Hydroxy*-p-*tolyl Cyanide*.—Dehydration of the oxime (Chuit and Bolsing, *Bull. Soc. chim.*, 1906, **35**, 134) (2 g.) of 3-hydroxy-*p*-tolualdehyde with boiling acetic anhydride (15 ml.) during 4½ hours gave 3-*acetoxy*-p-*tolyl cyanide* (1·1 g.) which formed needles, m. p. 58·5—59·5°, from light petroleum (b. p. 60—80°) (Found: C, 68·7; H, 5·1; N, 8·1%). On deacetylation with dilute sodium hydroxide this acetate gave the *hydroxy-cyanide* which separated from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 125° (Found: N, 10·4%).

The ultra-violet absorption spectra of the compounds recorded have been determined by Professor R. A. Morton of this University, to whom we express our thanks.

University of Liverpool. [*Received, July 29th*, 1948.]

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187. *Organic Sulphur Compounds. Part XXXI. Action of Heat on Some Free Radicals with Special Reference to the Free Phenylthiyl Radical.*

By Alexander Schönberg and Ahmed Mustafa.

When diphenyl disulphide is heated at 270°, thiophenol and diphenylene disulphide (I) (thianthren) are formed in good yield, believed to be produced from the free PhS· radical by disproportionation (see Scheme A). The formation of thiophenol or thiocresol by the heating of αβ-bisphenylthiostilbene (II*a*) or its analogues is explained similarly.

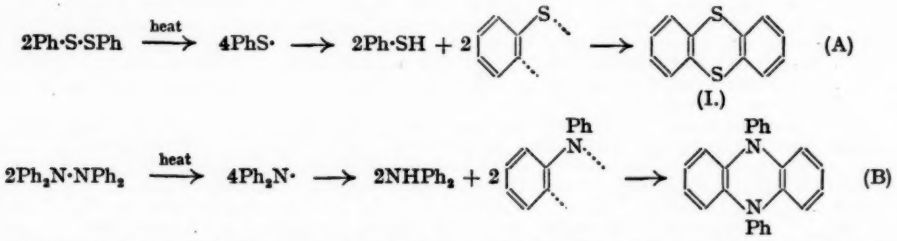
At 270°, reactions according to the Schemes (C) and (D) take place; they furnish further evidence for the tendency of free radicals to stabilise by disproportionation.

Some disulphides [*e.g.*, diphenyl disulphide and bisthionaphthoyl disulphide $(C_{10}H_7\cdot CS\cdot S\cdot)_2$] undergo with diphenyldiazomethane, hexaphenylethane, metal ketyls, metallic silver, and

triphenylphosphine reactions which lead to a cleavage of the ·S·S· group (Schönberg, Rupp, and Gumlich, *Ber.*, 1933, **66**, 1932; Schönberg, *Ber.*, 1935, **68**, 163). The question arises how these reactions are to be explained. One may argue (*a*) that in these aromatic disulphides the S–S linkage is abnormally weak (when compared with that in, *e.g.*, dimethyl disulphide) and that it is broken in these particular reactions; but it is also possible (*b*) that, especially at high temperatures, these aromatic disulphides dissociate with the formation of free radicals containing univalent sulphur ($RS{\cdot}SR \rightleftharpoons 2RS{\cdot}$) and that the above cleavages are brought about by the action of free radicals and not by the action of disulphides.

If the view (*a*) is accepted, then it is easy to imagine that in solution the " active " molecules (*i.e.*, only a small proportion of the total number) are dissociated to free radicals. Contrary to the views previously accepted (Lecher, *Ber.*, 1925, **58**, 417), it was pointed out for the first time by Schönberg (*Trans. Faraday Soc.*, 1934, **30**, 17; Schönberg *et al.*, *loc. cit.*) that diphenyl disulphide and related substances are capable of forming free arylthiyl radicals in hot solution. The dissociation theory of disulphides explains *inter alia* the thermochromic properties of diphenyl disulphide and the fact that its hot solutions do not obey Beer's law (Rupp, *Ber.*, 1933, **66**, 1933).

Pyrolysis should be a useful tool in deciding whether the formation of free radicals from disulphides actually takes place, taking into consideration the tendency of free radicals to stabilise according to the principle of disproportionation (see Scheme B, which shows the disproportionation reaction of diphenylnitrogen as formulated by Wieland, *Annalen*, 1911, **381**, 200). On the basis of the disproportionation theory, the formation of thiophenol and thianthren (I) from diphenyl disulphide at higher temperatures is to be expected, and this reaction actually occurs at 270°. Attention is drawn to the similiarity between Schemes (A) and (B); this analogy is a further indication that diphenyl disulphide forms free radicals at high temperatures, as do the tetra-arylhydrazines.



We have also found that, when αβ-bisphenylthiostilbene (II*a*) is heated at 270°, tolan is formed together with thiophenol, believed to be the stabilisation product of Ph·S·.

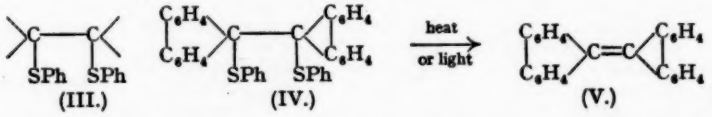
The formation of thiophenol was also observed in the case of αβ-*bisphenylthio*-αβ-*dicumylethylene* (II*c*). The formation of thio-*p*-cresol was observed when di-*p*-tolyl disulphide was heated at 270° and in the pyrolysis of αβ-*bis*-p-*tolylthiostilbene* (II*b*). In all these cases, the formation of thio-phenol or -*p*-cresol should be explained as occurring *via* the free arylthiyl radical.

Of the ethylenes previously mentioned, (II*a*) had been obtained by the action of thiophenol on benzoin in the presence of glacial acetic and hydrochloric acid (Posner, *Ber.*, 1902, **35**, 506) and the new ethylenes were prepared analogously.

$$R'{\cdot}C(SR){:}CR'{\cdot}SR$$

(II*a*; R = R′ = Ph. II*b*; R = *p*-Me·C_6H_4, R′ = Ph. II*c*; R = Ph, R′ = *p*-C_6H_4·$CHMe_2$.)

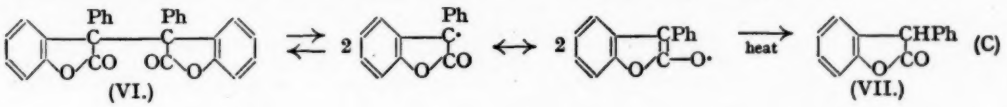
Recently, it has been shown that disulphides, believed to undergo dissociation into free radicals, react with olefins. Diphenyl disulphide, however, proved to be entirely without action on *cyclo*hexene at 180° (Bloomfield, *J.*, 1947, 1549). In this connection, it should be pointed out that substances containing the group (III) must be expected to be more or less thermolabile. For instance, (IV) is converted into (V) in boiling toluene in the dark and in

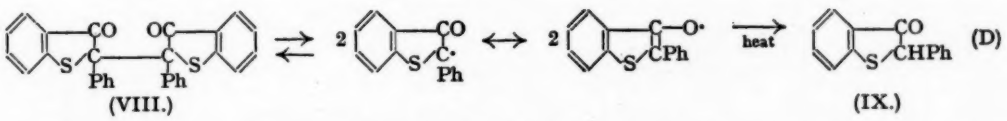


benzene at room temperature in the presence of light (Schönberg and Stolpp, *Annalen*, 1930, **483**, 90). Therefore, the fact that diphenyl disulphide does not add to the double bond with the

formation of substances stable at 180°, cannot be used as an argument against the theory that diphenyl disulphide and its analogues dissociate at higher temperatures.

Action of Heat on 2 : 2′-*Diketo*-3 : 3′-*diphenyl*-3 : 3′-*dicoumaranyl* (VI) *and* 2 : 2′-*Diphenyl-thioindigo-white* (VIII).—In connection with the above disproportionations, to which free radicals are liable, we have investigated the two substances (VI) and (VIII) which are known, in solution, to form free radicals that may be regarded as resonance hybrids and therefore as compounds containing a tervalent carbon atom or a univalent oxygen atom (Löwenbein and Simonis, *Ber.*, 1924, **57**, 2040; Kalb and Baeyer, *Ber.*, 1913, **46**, 3879). We have found that (VI) and (VIII) form the corresponding reduction products, namely, the lactone of *o*-hydroxy-diphenylacetic acid (VII) and 3-keto-2-phenyl-2 : 3-dihydrothionaphthen (IX), respectively, when heated at 270° without a solvent (see Schemes C and D, respectively).





Disproportionation Reactions of Biradicals.—The orange dehydroindigo breaks down at 195° into indigo on the one hand and higher oxidation products on the other (Kalb, *Ber.*, 1909, **42**, 3643). This behaviour cannot be forecast from the classical structural formula, but is in agreement with the radical formula (X) and recalls the formation of diphenylamine (see B).

The question whether dehydroindigo has a diamagnetic biradical structure or a paramagnetic one is left open. The former structure is one of the canonical structures among which the " normal " molecule resonates (see Szwarc, Faraday Society Discussion, 1947, No. 2, p. 78).

The term " biradical," introduced by the senior author (Schönberg and Vargha, *Annalen*, 1930, **483**, 179), may be defined as follows: " Biradicals are coloured substances which are similar in their chemical reactions to the triarylmethyl, diarylnitrogen, etc., radicals. They possess two centres of enhanced reactivity and are thermolabile. Their chemical behaviour cannot be expressed by structural formulæ based on the rules of classical organic chemistry."

This definition—in contradistinction to a definition based on the magnetic properties of compounds—allows the grouping under one heading of substances which are similar in their chemical reactions. For instance, dehydroindigo may be grouped with the violet pentacene, for which (XI) is the generally accepted formula. But pentacene undergoes disproportionation at 300° with the formation of 6 : 13-dihydropentacene (Clar, " Aromatische Kohlenwasserstoffe," p. 182, Berlin, 1941). Its formation recalls the synthesis of triphenylmethane when triphenylmethyl is heated (Wieland and Müller, *Annalen*, 1913, **401**, 235), and is in agreement with (XI*a*) (abbreviated formula for pentacene) but not with (XI).

Experimental.

Thermal Decomposition of Diphenyl Disulphide.—The pyrolysis was carried out in an apparatus similar to that employed for vacuum distillation (using a Liebig condenser) but without a capillary tube; the receiver was immersed in ice–salt. The pyrolysis flask (*A*) was in the form of a test-tube with a side tube; (*A*) was sealed after introduction of diphenyl disulphide (5·5 g.) and passage through it of a dry stream of carbon dioxide to replace the air. During pyrolysis (bath temp. 270°; 6 hours), the apparatus was connected to a water-pump. Drops were formed in the receiver, the smell of thiophenol was noticed, and the colour reaction with sodium nitrite in the presence of glacial acetic acid was obtained (Rheinboldt, *Ber.*, 1927, **60**, 184). Pyrolysis was thus carried out under conditions which allow thiophenol to escape as soon as formed. The drops collected were treated with benzoyl chloride in the presence of aqueous sodium hydroxide, and colourless crystals were obtained which, after recrystallisation from ethyl alcohol, were proved to be phenyl thiobenzoate (m. p. and mixed m. p.) (Found: C, 72·6; H, 4·9; S, 14·9. Calc. for $C_{13}H_{10}OS$: C, 72·9; H, 4·7; S, 14·9%). The yield was about 33% (after crystallisation), but the amount of thiophenol produced is higher than that calculated from the amount of ester obtained,

as the benzoylation is not quantitative. (Diphenyl disulphide was unaffected by benzoyl chloride under the same conditions.) The contents of (*A*) * were allowed to cool and a small quantity of alcohol was added. After standing at 0° overnight, colourless crystals were obtained and recrystallised from alcohol; they were proved by m. p. and mixed m. p. and the colour reaction with concentrated sulphuric acid to be thianthren (I); yield about 60% (Found: C, 66·5; H, 4·0; S, 29·2. Calc. for $C_{12}H_8S_2$: C, 66·7; H, 3·7; S, 29·6%).

Thermal Decomposition of pp'-*Ditolyl Disulphide.*—Similar thermal decomposition of this disulphide afforded thio-*p*-cresol (identified by m. p. and mixed m. p.).

Pyrolysis of αβ-Bisphenylthiostilbene (IIa).—This stilbene (3 g.) (Posner, *loc. cit.*) was subjected to pyrolysis as described above, and the formation of thiophenol was established in the same way. The contents of the pyrolysis flask were extracted several times with light petroleum (b. p. 30—50°) and on slow evaporation gave colourless crystals of tolan (m. p. and mixed m. p.).

*Preparation of αβ-Bis-*p*-tolylthiostilbene* (IIb).—Benzoin (5 g.) was dissolved in the minimal amount of glacial acetic acid, and treated with thio-*p*-cresol (7·8 g.). The reaction mixture was saturated with dry hydrogen chloride and sticks of anhydrous zinc chloride (cf. Posner, *loc. cit.*) were added. The mixture was kept overnight in an ice-chest, and colourless crystals separated; they were filtered off, washed with cold ethyl alcohol and with light petroleum (b. p. 30—50°), and crystallised from hot benzene; m. p. 170° (Found: C, 78·9; H, 5·5; S, 15·0. $C_{28}H_{24}S_2$ requires C, 79·2; H, 5·7; S, 15·1%). The *stilbene* was difficultly soluble in hot ethyl alcohol and light petroleum (b. p. 70—80°) and soluble in hot benzene. On pyrolysis as above, it gave thio-*p*-cresol (m. p. and mixed m. p.).

Preparation of αβ-Bisphenylthio-αβ-dicumylethylene (IIc).—Couminoin (5 g.) (Feigland *et al.*, *Ber.*, 1925, **58**, 2300), dissolved in the minimal amount of glacial acetic acid, was treated with thiophenol (5 g.) in the presence of dry hydrogen chloride, as described above. The crystals of the *ethylene* that separated from the mother-liquor (M) were filtered off, washed with light petroleum (b. p. 70—80°), and recrystallised from benzene; m. p. 182° (Found: C, 80·0; H, 6·7; S, 13·0. $C_{32}H_{32}S_2$ requires C, 80·0; H, 6·7; S, 13·3%). It was soluble in hot benzene and toluene and difficultly soluble in cold ethyl alcohol and light petroleum (b. p. 70—80°). On pyrolysis, (IIc) gave thiophenol (identified as phenyl thiobenzoate). The mother-liquor (M) was poured into water, and the mixture extracted with ether; the extract was washed with dilute aqueous sodium hydroxide solution then with water, and dried (Na_2SO_4). After evaporation of the ether, recrystallisation from hot benzene afforded more of the product.

Thermal Decomposition of 2 : 2'-*Diketo*-3 : 3'-*diphenyl*-3 : 3'-*dicoumaranyl* (VI).—This compound (1 g.) (Schönberg and Mustafa, *J.*, 1945, 660) was heated in a test-tube (*A*) connected by a bent tube to a similar tube (*B*) externally cooled by ice–salt. Facilities were provided to allow a stream of dry carbon dioxide to pass through the apparatus when air was displaced; then pyrolysis (bath temp. 270°) was carried out for ½ hour. Colourless crystals appeared on the walls of (*A*) and (*B*). They were collected, and recrystallised from benzene–light petroleum (b. p. 30—50°) in colourless crystals, m. p. 114°, proved to be the lactone of *o*-hydroxydiphenylacetic acid (VII) by m. p., mixed m. p., and colour reaction with sulphuric acid (Bistrzycki and Flatau, *Ber.*, 1895, **28**, 989).

Pyrolysis of 2 : 2'-*Diphenylthioindigo-white* (VIII).—This substance (0·5 g.) (Schönberg and Mustafa, *loc. cit.*) was subjected to pyrolysis as described for (VI). On the walls of tube (*A*), oily drops appeared which solidified on cooling. The solid crystallised from ethyl alcohol in colourless crystals, m. p. 105°, proved to be 3-keto-2-phenyl-2 : 3-dihydrothionaphthen (IX) by m. p., mixed m. p., and the colour reaction with sulphuric acid (Kalb and Baeyer, *loc. cit.*).

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188. *Organic Sulphur Compounds. Part XXXII. The Action of Triphenylphosphine on Organic Disulphides.*

By ALEXANDER SCHÖNBERG and MOHAMED ZAKI BARAKAT.

Tables I and II illustrate the different behaviour of certain disulphides towards triphenylphosphine. Diphenyl disulphide forms with triphenylphosphine an addition product which is easily hydrolysed. Table III illustrates the similarity between some reactions of disulphides and of halogens.

WHEREAS the disulphides listed in Table I are stable towards triphenylphosphine when heated in benzene solution, those listed in Table II undergo reaction affording the corresponding monosulphides and triphenylphosphine sulphide:

$$PPh_3\ (I.) + R{\cdot}S{\cdot}SR \longrightarrow PPh_3(SR)_2\ (II.)\dagger \longrightarrow PPh_3S\ (III.) + R{\cdot}SR$$

According to Pauling (" Fortschritte der Chemie Organischer Naturstoffe ", Vol. 3, p. 207, Vienna, 1939), phosphorus can form five covalent bonds. It is noteworthy that (III) is formed from (I) and (VII) even at 30° in carbon tetrachloride.

* This experiment was carried out by (Miss) Askar.

† This is to be regarded as including the form $\overset{+}{P}Ph_3{\cdot}SR(SR)^-$.

Diphenyl disulphide and (I) in boiling benzene form a product which when treated with water yields triphenylphosphine oxide and phenylthiol:

$$PPh_3 + Ph{\cdot}S{\cdot}SPh\ (IV.) \longrightarrow PPh_3(SPh)_2 \xrightarrow{H_2O} PPh_3O\ (V.) + 2Ph{\cdot}SH$$

It seems that the reaction takes place even at room temperature, for if a benzene solution of triphenylphosphine containing diphenyl disulphide is shaken with water, the latter turns acid.

The stability of the disulphides listed in Table I towards triphenylphosphine in boiling benzene may be due to the fact that they do not form free radicals in boiling benzene: $R{\cdot}S{\cdot}SR \rightleftarrows 2RS{\cdot}$. It is possible that the formation of (II) proceeds by the action of (I) on free radicals and not on undissociated disulphides (cf. Part XXXI, preceding paper).

In boiling benzene (VIII) and (IX) do not form the equilibrium $R{\cdot}S{\cdot}SR \rightleftarrows S + R{\cdot}SR$. This is proved by the fact that no phenyl *iso*thiocyanate is formed when the heating is carried out in the presence of phenyl *iso*cyanide; (III) and the monosulphide are therefore not formed from (I) and the disulphide in boiling benzene according to $R{\cdot}S{\cdot}SR \rightleftarrows R{\cdot}SR + S \xrightarrow{PPh_3}$ (III).

TABLE I.

Disulphides stable towards triphenylphosphine in boiling benzene: Diethyl (VI), dibenzyl, *oo'*-dinitrodiphenyl, *pp'*-dinitrodiphenyl, dibenzhydryl, dibenzthiazolyl, di-9-fluorenyl, diantipyryl.

TABLE II.

Disulphides which react with triphenylphosphine in boiling benzene: Bisthio-α-naphthoyl $(\alpha\text{-}C_{10}H_7{\cdot}CS{\cdot}S{\cdot})_2$ (VII), dibenzoyl (VIII), tetramethylthiuram, $(NMe_2{\cdot}CS{\cdot}S{\cdot})_2$ (IX), bis-*p*-dimethylaniline $(NMe_2{\cdot}C_6H_4{\cdot}S{\cdot})_2$ (X).

TABLE III.

Similarities in the action of certain organic disulphides with those of free halogens:

$$Ph{\cdot}S{\cdot}SPh\ (\text{or } I_2) + (Ar_3C{\cdot})_2 \longrightarrow 2CAr_3{\cdot}SPh\ (\text{or } 2CAr_3I)\ ^{1,2}$$
$$Ph{\cdot}S{\cdot}SPh\ (\text{or } I_2) + 2Ar{\cdot}\dot{C}(ONa)Ar' \longrightarrow 2Ar{\cdot}COAr' + 2SPhNa\ (\text{or } 2NaI)\ ^{3,4}$$
$$[\alpha\text{-}C_{10}H_7{\cdot}CS{\cdot}S{\cdot}]_2\ (\text{or } Br_2) + 2Ag \longrightarrow \alpha\text{-}C_{10}H_7{\cdot}CS{\cdot}SAg\ (\text{or } 2AgBr)\ ^{3}$$
$$Ph{\cdot}S{\cdot}SPh\ (\text{or } Br_2) + Ar_2CN_2 \longrightarrow N_2 + CAr_3(SPh)_2\ (\text{or } CAr_2Br_2)\ ^{5,6}$$
$$Ph{\cdot}S{\cdot}SPh\ (\text{or } Cl_2) + PPh_3 \longrightarrow PPh_3(SPh)_2\ (\text{or } PPh_3Cl_2)\ ^{7}$$

[1] Schönberg *et al.*, *Ber.*, 1933, **66**, 242. [2] Gomberg, *Ber.*, 1900, **33**, 3158. [3] Schönberg *et al.*, *Ber.*, 1933, **66**, 1932. [4] Schlenk and Weickel, *Ber.*, 1911, **44**, 1185. [5] Staudinger and Gaule, *Ber.*, 1916, **49**, 1956. [6] Schönberg *et al.*, *Ber.*, 1929, **62**, 440; 1930, **63**, 3102. [7] Cf. Schönberg, *Ber.*, 1935, **68**, 163.

EXPERIMENTAL.

The benzene used was thiophen-free and dried over metallic sodium. When the solutions of the reactants were heated under reflux, the condenser was fitted with a calcium chloride tube and the reagents were protected from direct sunlight. All reaction products were identified by m. p. and mixed m. p. determinations.

Purification of Triphenylphosphine.—A solution of triphenylphosphine (10 g.) in benzene (50 c.c.) was shaken twice with concentrated hydrochloric acid (50 c.c.). The acid layer was separated and distilled water was added until further addition no longer produced a deposit. The mixture was kept for several hours in the dark in a closed vessel, then filtered, and the residue was washed until the washing water was neutral to litmus. Triphenylphosphine was dried in a vacuum over potassium hydroxide and then over phosphoric oxide.

Reaction of Disulphides listed in Table II with Triphenylphosphine.—(*a*) The phosphine (1 mol., 2·62 g.) and (IX) (1 mol.) in benzene (30 c.c.) were heated under reflux for 8 hours. The solution was then allowed to cool, and the benzene driven off in a vacuum. The residue consisted of almost colourless and of yellow crystals. It was powdered and boiled for 15 minutes with distilled water (200 c.c.); the yellow solution was filtered while hot, and on cooling, the filtrate deposited yellow crystals which, recrystallised from dilute alcohol, were proved to be tetramethylthiuram monosulphide (2·1 g.). The triphenylphosphine sulphide (III) did not dissolve in the water and was obtained in nearly theoretical yield.

(*b*) Similarly, (VIII) (2·5 g.) and (I) (2·39 g.) in benzene (50 c.c.) yielded after 12 hours (III) (2·3 g.) and dibenzoyl sulphide (1 g.); also (I) (1 mol., 2·1 g.) and (X) (1 mol.) in benzene (50 c.c.) yielded after 10 hours (III) (1·2 g.) and bis-*p*-dimethylaniline sulphide, $(NMe_2{\cdot}C_6H_4)_2S$ (1·2 g.).

(*c*) The phosphine (I) (1 mol., 1·31 g.) and (VII) 1 mol.) in carbon tetrachloride (75 c.c.) were kept for 8 days in a closed vessel at about 30°. The solvent was distilled off in a vacuum, and the residue extracted with light petroleum. The remainder was crystallised from carbon tetrachloride, giving triphenylphosphine sulphide (1·10 g.).

Triphenylphosphine and Diphenyl Disulphide.—(*a*) The phosphine (1 mol., 2·4 g.) and the disulphide (1 mol.) in benzene (80 c.c.) were heated under reflux for 14 hours. The solution was then allowed to cool and extracted with 8% sodium hydroxide solution (20 c.c.) for 15 minutes in a separating funnel.

The alkaline aqueous layer was separated, washed with benzene (10 c.c.), and then separated again. Benzoyl chloride (2 c.c.) was added, and the mixture shaken vigorously in a closed vessel. An oil which separated out was isolated and on standing for 3 days it crystallised; the solid was filtered off, washed thoroughly with distilled water, dried, and recrystallised from alcohol. Colourless crystals, m. p. 56°, were obtained and proved to be phenyl thiobenzoate (0·64 g.). The benzene layer was washed with distilled water, dried (Na_2SO_4), filtered, and the benzene driven off; the remaining oil solidified on standing. This solid was heated at 100° for about 30 minutes to dehydrate the hydrate of triphenylphosphine oxide and then crystallised twice from light petroleum (b. p. 80—100°); the oxide (1 g.) separated out.

(*b*) Triphenylphosphine (1 mol., 2·62 g.), diphenyl disulphide (2·18 g.), benzene (35 c.c.), and distilled water (20 c.c.) were heated under reflux for 14 hours, then allowed to cool; the aqueous layer was separated from the benzene layer, which was shaken with concentrated aqueous ammonia, the extract being added to the aqueous layer, which was then filtered and allowed to react with the oxygen of the air, the disulphide (0·55 g.) being recovered. The remaining benzene layer was evaporated to dryness. A brown oil was obtained which solidified on standing and from which triphenylphosphine oxide (1·4 g.) was obtained and identified as above.

(*c*) In one of three similar flasks, each fitted with a stopper, were placed benzene (30 c.c.), triphenylphosphine (1 mol., 2·6 g.), diphenyl disulphide (1 mol.), and distilled water (95 c.c.), previously boiled to free it from carbon dioxide; after one hour's shaking in the dark, the aqueous layer was acid to litmus. At the same time two parallel experiments were done exactly as above, one without the phosphine and the other without the disulphide. In both cases the aqueous layer was neutral to litmus before and after one hour's shaking.

Inactive Disulphides.—The lack of reaction between these disulphides (Table I) and triphenylphosphine was investigated by 10 hours' boiling in benzene solution; in the case of (VI) the experiment was performed at about 98° in a sealed tube.

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189. *A Torsion Microbalance for Measuring Low Pressures of Monolayers.*

By MIRKO KALOUSEK.

A description of the apparatus and technique for measuring low surface pressures of monolayers is given. A fibre loop on the surface of a liquid contains a reference monolayer, and the monolayer to be studied is spread outside. If the ring is held at one end of a diameter and pulled at the other, the fibre forms two arcs of a circle. The difference of pressure within and outside the loop is measured by the tension required for extension. In the apparatus the tension required is measured by a torsion wire.

APPARATUS for measuring low pressures of monolayers are generally of two types: the hanging-plate type and the surface-balance type. The former, introduced by Dervichian (*J. Phys. Radium*, 1935, **6**, 221, 429) and Harkins and Anderson (*J. Amer. Chem. Soc.*, 1937, **59**, 2189), was used by Bull (*ibid.*, 1945, **67**, 4, 5) for measuring the surface pressure of protein films. The method is simple and, when properly used, reliable. It requires, however, precise temperature control and a careful choice of material for the hanging plate, since a small change of wetting angle owing to the deposition of a monolayer may introduce large errors.

These apparatus have in common the division of the liquid surface into two parts: the substance to be studied is spread on one part, while the other part is kept at a constant surface pressure, usually as low as possible. The difference in pressure between the two parts is compensated for by means of a known force. In apparatus of the Langmuir type, adapted for measuring small surface pressures by Adam and Jessop (*Proc. Roy. Soc.*, 1926, *A*, **110**, 423) and slightly improved by Harkins (see Weiseberger, "Physical Methods of Organic Chemistry," Interscience Publishers, N.Y., 1945), these two parts are divided by a mica barrier and thin threads covered with vaseline. The necessity of keeping the water level constant makes satisfactory cleaning of the surface impossible in this type of apparatus, and it is also difficult to prevent leakage at the connections between the floating barrier and the threads.

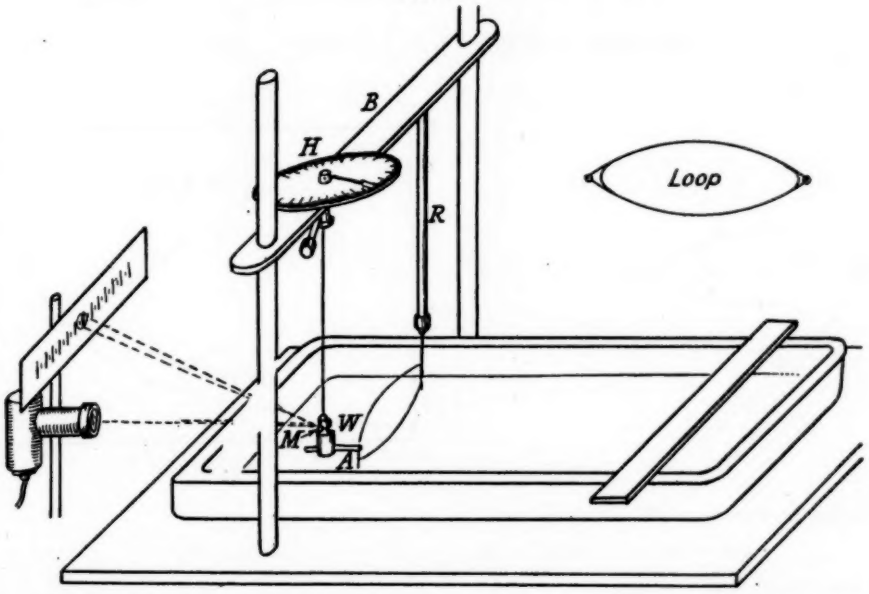
The most sensitive apparatus, developed by Guastalla (*Cahier de Physique*, 1942, **10**, 36), enables pressures of the order of millidynes/cm. to be measured. The two parts of the surface are separated by a vaselined thread which is kept in tension by an arm attached to a weight hung on a torsion wire. The pressure difference forces the thread into the arc of a circle. As long as the displacement of the thread is small, it is proportional to the pressure difference, at constant tension; or, for a constant displacement, the pressure difference is proportional to the tension. Disadvantages of this method are the possibility of leakage at the solid–thread connections and the relatively complicated optical system necessary to obtain sufficient accuracy. The necessity of keeping the level constant was avoided by the introduction of a

floating frame. It is, however, regrettable that a more complete description of experimental details has not been published.

As none of the above methods was entirely satisfactory for measuring surface pressures of the order of 10^{-3} dyne/cm., a new method has been developed.

Principle of the Method.—A thread is tied in a closed loop and placed on the surface of the water; when this is done properly there is no leakage between monolayers inside and outside the loop. If the film inside has the greater surface pressure the loop becomes circular so as to enclose the maximum area. If one point of the loop is fixed and the point opposite is pulled, the loop is forced into the form of two arcs of a circle, again enclosing the maximum area possible. The tension is applied to the loop by means of an arm attached to the weight W, hung on a torsion wire (Fig. 1). When this arm is kept in a fixed position the tension is proportional to

FIG. 1.



the angular displacement of the torsion head. Thus the force required to keep the loop at a constant length can be measured by the torsion required to keep the position of the weight as indicated by the light spot, and hence the difference in pressure can be calculated. During the experiment it is necessary to have a monolayer inside the loop whose surface pressure is constant, greater than that of the outside monolayer to be studied.

Derivation of Fundamental Relations.—For the loop formed by two arcs of a circle according to Fig. 2, we have

$$l = R\phi \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$a = R \sin \frac{\phi}{2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The relation between the surface pressure π and the force f can be calculated from the condition that the work necessary to expand the loop is equal to the work necessary to compress the film; *i.e.*,

$$-\pi . \, dA = 2f . \, da \text{ or } \pi = -2f/(dA/da) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where A is the area enclosed by the loop, so that

$$\tfrac{1}{2}A = \tfrac{1}{2}\phi R^2 - aR \cos \frac{\phi}{2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4a)$$

Substituting from equations (1) and (2), we obtain

$$\tfrac{1}{2}A = \tfrac{1}{2}lR - a(R^2 - a^2)^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4b)$$

and after differentiation and rearrangement

$$\tfrac{1}{2}(dA/da) = (dR/da)[\tfrac{1}{2}l - aR(R^2 - a^2)^{-\frac{1}{2}}] + (R^2 - a^2)^{-\frac{1}{2}}(2a^2 - R^2) \quad . \quad . \quad (5)$$

From equation (1), since l is constant, we have

$$d\phi/da = -(\phi/R)(dR/da) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

and from equation (2)

$$1 = \sin\frac{\phi}{2}\cdot\frac{dR}{da} + \frac{1}{2}R\cos\frac{\phi}{2}\cdot\frac{d\phi}{da} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Substituting for $d\phi/da$ from equation (6) in equation (7), we get

$$1 = \sin\frac{\phi}{2}\cdot\frac{dR}{da} - \frac{1}{2}\phi\cos\frac{\phi}{2}\cdot\frac{dR}{da}$$

which, on elimination of ϕ and rearrangement, gives

$$1 = \frac{1}{R^2}(R^2 - a^2)^{\frac{1}{2}}[aR(R^2 - a^2)^{-\frac{1}{2}} - \tfrac{1}{2}l]\frac{dR}{da}$$

or

$$(dR/da)[\tfrac{1}{2}l - aR(R^2 - a^2)^{\frac{1}{2}}] = -R^2(R^2 - a^2)^{-\frac{1}{2}}$$

FIG. 2.

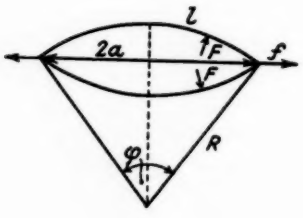
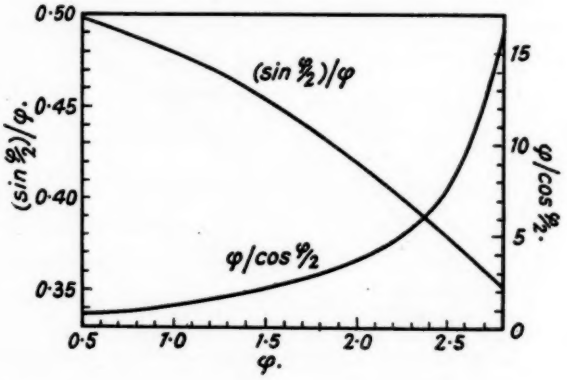


FIG. 3.



Substituting in equation (5), we then have

$$\tfrac{1}{2}(dA/da) = -R^2(R^2 - a^2)^{-\frac{1}{2}} + (R^2 - a^2)^{-\frac{1}{2}}(2a^2 - R^2) \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and by rearrangement

$$dA/da = 4(R^2 - a^2)^{\frac{1}{2}}$$

which, introduced into equation (3), gives

$$\pi = \tfrac{1}{2}f(R^2 - a^2)^{-\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Substitution of $(R^2 - a^2)^{-\frac{1}{2}} = (\phi/l)/\cos\frac{\phi}{2}$ from equations (1) and (2) gives the final relation between the pressure of the film inside the loop and the force applied to the loop, *viz.*:

$$\pi = (f\phi/2l)/\cos\frac{\phi}{2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9a)$$

In practice, $(\sin\frac{\phi}{2}/\phi)$ is calculated from the known values of a and l, and the value of $\phi/\cos\frac{\phi}{2}$ is obtained for the same value of ϕ from the graph (Fig. 3).

The area enclosed by the loop may be calculated from equation (4*b*), which may be written as

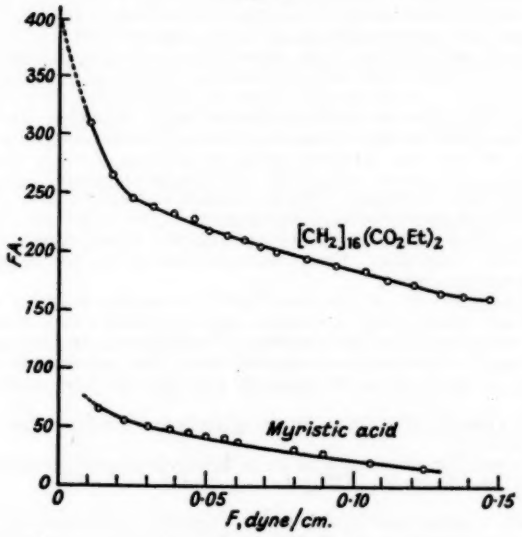
$$A = \frac{l^2}{\phi} - 2al\frac{\cos\frac{\phi}{2}}{\phi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4c)$$

Equation (9*a*) shows that the highest sensitivity is obtained for small values of $\phi/\left(\cos\frac{\phi}{2}\right)$, which are obtained with an elongated loop. Work in this region, on the other hand, suffers from the disadvantage that a small change of the length corresponds to a big change in the area

enclosed by the loop. This substantially changes the pressure of the film inside the loop which decreases the sensitivity of the adjustment of the constant length of the loop. In the apparatus described, the angle ϕ was approximately 1·5 radians, corresponding to a value of approximately 2 for $\phi/\cos\frac{\phi}{2}$.

An important factor in determining the sensitivity of the apparatus is the choice of the substance to be spread inside the loop. As mentioned above, the pressure inside the loop should change as little as possible with change of area. This limits the choice of material to those giving a gaseous or expanded film at pressures of 0·2—0·3 dyne/cm. Ethyl hexadecane-1 : 16-dicarboxylate was found to be satisfactory for this purpose. The sensitivity of the apparatus described (3×10^{-3} dynes/cm./div.) was found to be within the experimental errors of the rest of the experiment, *viz.*, cleaning the air, water, and solvent, and measurement of the volume of solution injected.

FIG. 4.



EXPERIMENTAL.

Description of the Apparatus.—The balance is shown diagrammatically in Fig. 1. The horizontal brass bar (*B*), which carries the torsion head (*H*) and the brass rod (*R*) supporting one end of the loop, is fixed to the top of the box in which the trough is contained. The rod *R* may be moved in the horizontal plane so that the loop can be adjusted to the desired length. The torsion head is divided into 180 divisions so that each division is equal to 2°. The concave mirror (*M*) and a horizontal arm (*A*), which is of adjustable length and holds the pin supporting the movable end of the loop, are attached to the torsion weight (*W*).

The loop is made of nylon thread, approximately 0·01 mm. thick, but, *e.g.*, terelin or polythene could be used, provided the thread is thin and strong enough.

Experience showed that to prevent leakage there must be no knots or crossings of fibres in the loop, and the fibre must be sufficiently hydrophobic. To ensure that the two arcs of the loop are equal, the loop was made from two fibres of equal length connected to two small circles of polythene with the hole for the needle in the middle (Fig. 1, inset). To prevent leakage at the fibre–polythene connections, these were protected by means of another fibre which was stuck to those forming the loop.

As the surface of nylon was not sufficiently hydrophobic, it had to be covered with the thin layer of a strongly hydrophobic substance. Vaseline, which is recommended by many authors, was found to be unsatisfactory because it spreads slightly itself and because it does not stick to the surface of the fibre very well. The best results were obtained with Everet's Vacuum Wax (No. 2, soft 60°). A thin layer of wax is put on the thread by means of a hot rod covered in molten wax. As temperature changes and contact with water cause the fibre to shrink, it is necessary to wet the fibre which is to be used for making the loop repeatedly with the molten wax to shrink it beforehand. For precise measurements it is still necessary to measure the total length from time to time and to allow for any alteration.

The air in the box, which enclosed the trough, was pumped out with the same water pump that was used for cleaning the surface, purified by bubbling through a column of dilute potassium hydroxide and water, and blown back into the box. The solution of the substance to be spread was injected on the water surface from an " Agla " microsyringe with a long thin needle which was inserted through a sheet of rubber covering a small window in the front of the box.

Calibration.—The torsion wire was calibrated by the swinging method. When the wire is twisted

through 2° the force f at the end of the torsion arm is given by $f = \pi^2 I/90\, t^2 d$, where I is the moment of inertia of the torsion arm and weight, d the length of the torsion arm, and t the period of swing. The moment of inertia of the torsion arm and weight was found by determining the period of swing of the torsion weight with the period of swing of another torsion weight the moment of inertia of which it was possible to compute. Then $I/I_0 = t^2/t_0^2$, where I_0 is the moment of inertia of a torsion weight used for calibration and t_0 is its period of swing.

In the apparatus described, the moment of inertia of the torsion weight I was 6·16 g.-cm.^{2} when the arm was adjusted to a length of 3 cm. The total weight was 18 g. The torsional force at the end of the arm was $5{\cdot}18 \times 10^{-3}$ dyne/2° twist. The length of the arcs l was measured directly and found to be 16·2 cm. The length of the loop, $2a$, was measured directly on the water. A polythene scale with two incisions a distance of $2a$ apart and a perpendicular arm was placed on the surface of the water. The two needles supporting the ends of the loop were placed in the incisions, the rod R was moved until the torsion arm was parallel to the perpendicular arm of the scale, and the zero position of the spot of light noted. A correction was made for the two polythene circles; $2a$ was equal to 14·6 cm.

The difference of surface pressure for a 2° twist of the torsion wire was $\pi = 3{\cdot}36 \times 10^{-3}$ dynes/cm./2°.

Cleaning the Surface.—It was found that even freshly distilled water contains an appreciable amount of surface-active material. This can be proved by spreading used mineral oil on the surface: a clean surface is completely covered by the oil which exhibits interference colours. The oil does not, however, spread completely on a contaminated surface, and the contaminated areas appear as black spots.

The surface could not be cleaned sufficiently with moving barriers for a variety of reasons. Guastalla (*loc. cit.*) describes a method where talc, previously cleaned by heating, is spread on the surface and then blown into a corner of the trough by a cleaned air stream, where it is sucked off together with the impurities and a little water. It was found, however, that the talc particles contaminated the film inside the loop and formed bridges across the fibre, causing slight leakage. The method adopted was to collect impurities in a corner of the trough by blowing with a clean air stream and to suck them off as in Guastalla's method. The process was repeated until the surface pressure attained a constant value.

The contamination of the surface was reduced to a minimum by carefully cleaning the air in the box, described above, the trough, and the liquid. A silica trough was used which, after being cleaned in the usual way, was heated to red heat before each experiment. The water used was distilled twice in an all-glass apparatus made of Pyrex glass, the second distillation being from a dilute solution of barium hydroxide as recommended by Guastalla. Under these conditions the rate of change of surface pressure was less than 1×10^{-3} dyne/cm./min.

Spreading of Films.—From the above it is clear that it is possible to study monolayers at these low pressures only when they are spread from a solution whose solvent either does not affect the surface tension or evaporates in 1—2 minutes. This condition is fulfilled with light petroleum (b. p. 70°) which, in amounts of 1 mm.^{2}/100 cm.^{2} evaporates in about 1 minute. The same amount of benzene appreciably altered the surface tension of water after 10 minutes, and the effect of acetone or amyl alcohol was detectable after an hour.

It is probable that some protein films may be completely spread from their solutions in water, but this has not yet been proved.

The *FA–F* curves obtained for myristic acid on N/100-hydrochloric acid and for the dibasic ester ethyl hexadecanedicarboxylate are shown in Fig. 4.

The work described was carried out in the Davy–Faraday Laboratory of the Royal Institution, London, and my thanks are due to Prof. E. K. Rideal, F.R.S., for suggesting the method and his kind encouragement and to Dr. R. S. Rivlin for his assistance with the mathematics involved. I would also like to thank the British Council for a scholarship which enabled me to carry out this work.

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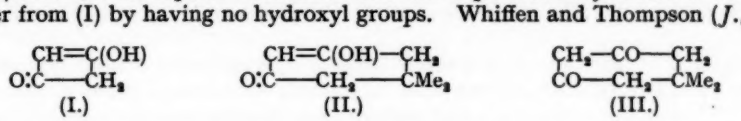
190. "*Dimedone*" *and its Monoethyl Ether.*

By A. A. HUKINS and R. J. W. LE FÈVRE.

Chemical evidence shows that ordinary "dimedone" reacts readily as the mono-enol (II), the structure of which is taken as a model for the formula (I) previously proposed for diketen. The moment of dimedone, in benzene solution, is *less* (3·5 as against 3·8 D.) than that of its ethyl ether. This is the reverse of the order commonly found for monohydric alcohols, phenols, etc., and the corresponding R·OEt derivatives, but resembles the situation found for salicylaldehyde, quinol, and the carboxylic acids. The infra-red spectra in carbon tetrachloride of dimedone and ethyl acetoacetate are roughly similar between 2·6 and 3·0 μ and indicate the presence of hydroxyl groups. Under the conditions of measurement, dimedone is unlikely to be entirely diketonic. The observed moments are explicable if the monoenolic hydroxyl group lies in the plane containing the ethylenic double bond.

ANGUS, LECKIE, LE FÈVRE, LE FÈVRE, and WASSERMANN (*J.*, 1935, 1751), finding the dipole moment of dimeric keten to be $3{\cdot}1_8$ D. (in benzene) or $3{\cdot}3_0$ D. (in carbon tetrachloride), concluded that, of the then extant formulæ, (I) appeared most nearly correct. Later, others were advanced by Hurd *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 962; 1939, **61**, 3355; 1940, **62**, 1147, 1941, **63**, 2174) and Boese (*Ind. Eng. Chem.*, 1940, **32**, 16), which, as Oesper and Smyth (*J. Amer. Chem. Soc.*,

1942, **64**, 768) noted, also required moments near the experimentally observed value. These formulæ differ from (I) by having no hydroxyl groups. Whiffen and Thompson (*J.*, 1946, 1005)



(I.) (II.) (III.)

have more recently reported that the infra-red and Raman spectra of dimeric keten do not show the usual indications of associated or unassociated hydroxyl.

The present measurements were initiated following discussions on the above evidence with Dr. A. Wassermann. He pointed out that, on the basis of (I), dimeric keten would be distinguished from the common β-diketones in that, unless unusual distortions of intervalency angles are supposed, (I) cannot develop an internal O . . . H . . . O bridge, so that the absence of *certain* spectral features characteristic of ordinary enols might therefore be expected. For this reason it seemed of interest to examine another molecule having the same stereochemical limitation as (I).

Dimedone appeared suitable. The summary of its chemistry in Beilstein's "Handbuch" (VII, 599; VII*, 313; VIII, 6) revealed a readiness to undergo reactions as a mono-enol (II), an inspection of models of which confirmed the difficulty of bringing the hydroxylic hydrogen into adequate proximity to the ketonic oxygen.

We give below new data for (*a*) the dipole moment of dimedone and of its monoethyl ether, and (*b*) its infra-red spectrum. For comparison, the spectra of ethyl acetoacetate, salicylaldehyde, phenol, and *p*-cresol are included.

Dipole-moment Determinations.—Dimedone and its monoethyl ether were prepared by the methods cited in Beilstein (*op. cit.*). The apparatus, technique, and symbols used have been described before (cf. *J.*, 1948, 1949). Measurements are relative to benzene, for which $\varepsilon_{1000\text{ kc.}}^{25°} = 2{\cdot}2725$ and $d_4^{25°} = 0{\cdot}87378$.

	Dimedone.				Dimedone ethyl ether.			
$100w_1$	0·1480	0·1837	0·1953	0·2486	0·3908	0·9337	1·5138	2·2632
$\varepsilon_{1000\text{ kc.}}^{25°}$	2·2850	2·2905	2·2923	2·2960	2·3095	2·3565	2·4094	2·4757
$d_4^{25°}$	0·87407	0·87419	0·87417	0·87420	0·87412	0·87468	0·87527	0·87602

	M.	Mean $\alpha\varepsilon_1$.	Mean β.	$_\infty P_1$ (c.c.).	$[R_L]_D$ (c.c.).	μ, D.
Dimedone	140	9·46	0·225	286	38	3·46
Dimedone ethyl ether ...	168	9·12	0·109	339·2	47	3·76

The moments of dimedone and of its ethyl ether are related in an unusual manner. Normally, the moments of alcohols and phenols are greater than those of their ethers. Among the hydroxylic compounds resembling dimedone in this respect may be noted salicylaldehyde ($\mu = 2{\cdot}9$ D.) and *o*-methoxybenzaldehyde ($\mu = 4{\cdot}1$ D.) (Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 1835), quinol and its dimethyl ether (Lander and Svirbely, *J. Amer. Chem. Soc.*, 1945, **67**, 332), and the lower fatty acids and esters (cf. *Trans. Faraday Soc.*, 1934, Appendix).

However, there is no extant evidence to suggest that dimedone in dilute benzene solutions is 100% mono-enolised. Since 3 : 3-dimethyl*cyclo*hexanone has $\mu = 2{\cdot}92$ D. (Hassel and Naeshagen, *Z. physikal. Chem.*, 1932, *B*, **19**, 434), dimedone, were it a pure diketone, should, by elementary structural and vectorial considerations, have much the same value. The greater moment now found, *viz.*, 3·5 D., is therefore an *indication* that dissolved dimedone is not entirely in the diketo-form. The mono-enol most probably contains a conjugated system, the effect of which is seen in 3 : 5-dimethyl*cyclo*hex-5-en-1-one ($\mu = 3{\cdot}8$—$4{\cdot}0$ D., compared with 3 : 5-dimethyl*cyclo*hexan-1-one, $\mu = 2{\cdot}9$ D.; Hassel and Naeshagen, *loc. cit.*). Speculation concerning the possible moment of the mono-enol would accordingly be of little use. Nevertheless, that this should be *higher* than μ_{diketo} is plausible, and that it should be *lower* than $\mu_{\text{mono-enol ether}}$ is (see later) understandable.

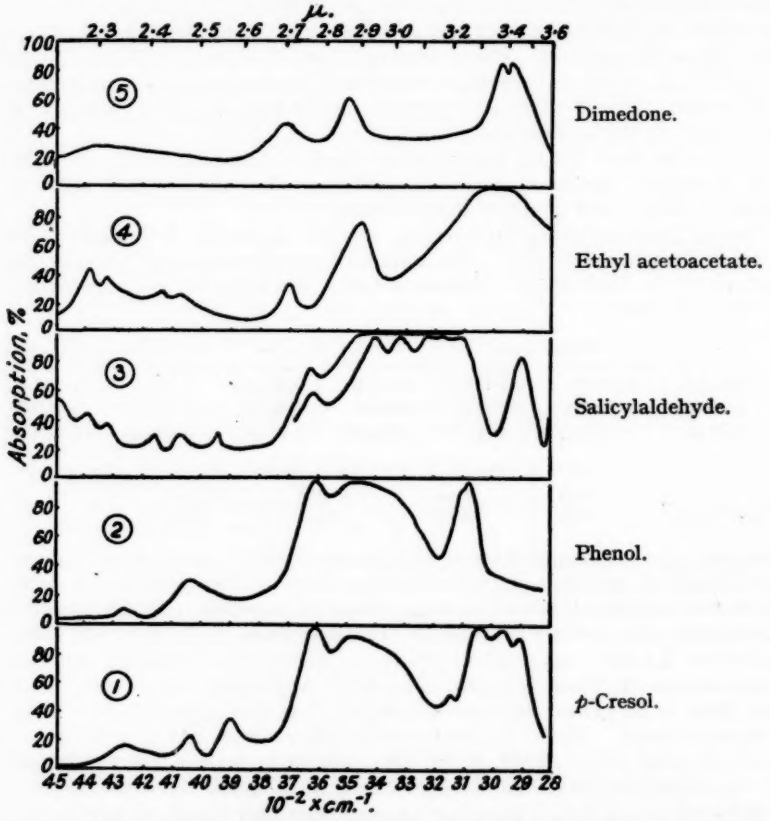
Infra-red Spectra.—Nearly saturated solutions in carbon tetrachloride of dimedone, ethyl acetoacetate, salicylaldehyde, phenol and *p*-cresol were examined, as described by Anderson, Le Fèvre and Savage (*J.*, 1947, 448). Solvent and solutes were dried and/or redistilled, as appropriate, immediately before use. The plots of absorption against wave-length are reproduced in the figure.

Discussion.—Curves (1) and (2) are in satisfactory agreement with the results of Fox and Martin (*Proc. Roy. Soc.*, 1937, *A*, **162**, 419) and provide "bench marks" for the remaining substances. These authors (*Trans. Faraday Soc.*, 1940, **36**, 897) list the following absorptions to be expected for compounds containing hydroxyl groups: 2·765 μ for monomeric hydroxyl,

with a " modification " at 2·776—2·807 μ, 2·865 μ fo dimeric hydroxyl, and 2·987—3·006 μ for polymeric hydroxyl. The intramolecular O–H bond in methyl salicylate is prominent at 3·122 μ.

The absorption around the last quoted frequency is intensely shown by our results for salicylaldehyde. It is notably absent with dimedone, as anticipated from our introductory premise (p. 897), and also with ethyl acetoacetate, an observation which is undergoing further investigation.

Bawn (*J.*, 1932, 1189) concluded " that the normal hydroxyl vibration existing in the alcohols is not present in the infra-red spectra of the enolic forms of certain tautomeric compounds ". Ethyl acetoacetate was among the substances examined. He found absorption at 2·9 μ but associated it with the carbonyl group. However, Kohlrausch and Dadieu (*Ber.*, 1930, **63**, 1657; Kohlrausch, " Smekel-Raman Effekt ", Berlin, 1931; *J. Opt. Soc. Amer.*, May,



1931) had previously described the Raman spectrum of ethyl acetoacetate, identified certain shifts with the C=O and C=C linkages, and reported a hydroxyl band at 3380 cm.$^{-1}$ as present although very faint. The last had been undetected by Venkateswaran and Bhagavantam (*Indian J. Physics*, 1930, **5**, 129). For these reasons we have included ethyl acetoacetate as well as dimedone in our figure; both show absorption in the 2·6—3·0 μ region. The weaker band in each case occurs just under 2·70 μ. With dimedone the stronger lies at 2·86—2·87 μ, and with ethyl acetoacetate at 2·89—2·90 μ.

The band at 2·70 μ is somewhat unexpected. Davies (*Trans. Faraday Soc.*, 1940, **36**, 333) reports it also for carbon tetrachloride–chloral hydrate mixtures, but ascribes it to an overtone or combination characteristic of $-CCl_3$. Fox and Martin (*loc. cit.*) note that wet benzyl alcohol absorbs at 2·698 and 2·776 μ, whereas the carefully dried liquid absorbs at the latter wave-length only. It is difficult to be certain that our result is not similarly due to traces of moisture; however, our materials were redistilled immediately before use and the solvent in all five cases had been prepared and stored uniformly. There is no sign of absorption at this point in three of our spectra.

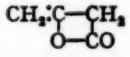
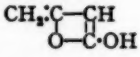
Peaks between 2·8 and 2·9 μ are clearly reconcilable with the presence of hydroxyl—possibly dimeric (cf. Fox and Martin, *loc, cit.*), although carboxylic hydroxyl absorbs at 2·84 μ, the hydroxyl of chloral hydrate at 2·82 μ (Davies, *loc. cit.*), and that of phenol in several solvents at 2·79 and 2·96 μ (Gordy and Nielsen, *J. Chem. Physics*, 1938, **6**, 12). Particularly relevant seem the observations of Buswell, Rodebush, and Whitney (*J. Amer. Chem. Soc.*, 1947, **69**, 770) on certain vinyl alcohols stabilised against enol-keto rearrangement by the steric hindrance of substituent groups. These compounds all showed weak absorption around 2·76 μ (*i.e.*, where monomeric O–H is expected to display itself) and stronger absorption at 2·84 to 2·86 μ. Wulf, Liddel, and Hendricks (*J. Amer. Chem. Soc.*, 1936, **58**, 2287) had earlier found *o*-chlorophenol to absorb at 2·775 and 2·825 μ, while Davies (*loc. cit.*) had similarly reported 2·782 and 2·84 for *o*-bromophenol, and 2·775 and 2·896 for benzoin. These authors explain their results by suggesting that the hydroxyl group can adopt coplanar configurations with respect to its oxygen and the two carbons of the double bond (cf. Pauling, *J. Amer. Chem. Soc.*, 1936, **58**, 94). There are thus two positions for the hydrogen atom. That in which it is more remote from the ethylenic linkage (" *trans* ") is identified with the normal frequency 2·76 μ, but this being always the weaker of the two absorptions, the inference is drawn that the *cis*-configuration has, in each case, the lower energy, and, at ordinary temperatures, is therefore the form which predominates.

If we may assume that the absorption between 2·86 and 2·87 μ in dimedone corresponds to the longer wave-band for each of the molecules just quoted, a *qualitative* explanation can be provided of our dipole-moment results. The mono-enolic form of dimedone will exist chiefly as " *cis*-enol " in which the H–O–C resultant moment operates to some degree against the C=O moment. Ethylation should destroy the factors (? a type of hydrogen-bond formation with C=C) which stabilise the *cis*-forms, and in many of the infinitude of configurations available to the ethoxy-group during " free " rotation, a resultant C–O–C moment will augment the C=O moment.

Dimeric Keten.—When we first read Whiffen and Thompson's paper (*loc. cit*) we suspected that the infra-red spectrum of dimeric keten there reported did not incontrovertibly exclude the participation of (I) in the manner set out by the University College authors (*J.*, 1935, 1751). In particular, we felt that any absorption between the approximate limits 2·9 and 2·7 μ (3440 and 3700 cm.$^{-1}$), even if weak, might be evidence of hydroxyl. Two such bands (at 3370 and 3620 cm.$^{-1}$) *were* listed (Whiffen and Thompson, *loc. cit.*, p. 1007), as " very weak bands . . . much more reasonably interpreted as overtones and combinations ". Further, Whiffen and Thompson also noted that the absorptions at 1865 and 1895, and 1685 and 1705 cm.$^{-1}$ varied in relative intensity in different solvents. In the discussion, these frequencies were associated with C=O and C=C stretching vibrations. Now, Meyer with Kappelmeier (*Ber.*, 1911, **44**, 2718; 1912, **45**, 2852) and Schoeller (*Ber.*, 1920, **53**, 1410) had demonstrated the marked sensitivity to solvents of keto-enol equilibria, and if dimeric keten contained the $\cdot CH_2 \cdot CO \cdot$ unit, replacement of chloroform as a medium by carbon tetrachloride, would, by analogy, probably increase the percentage of enol, and thus cause change in the appropriate intensities.

However, in view of the definite absorptions now observed with two authentic keto-enolic substances, we are inclined to concur with Whiffen and Thompson's explanation of the bands at 3370 and 3620 cm.$^{-1}$ and to agree that their work dismisses formula (I).

Since our experiments were concluded, we have had the advantage of perusing the MS. of a recent paper by Dr. A. Wassermann (*J.*, 1948, 1323) on the acidity of dimeric keten. He concludes

(IV.)   (V.)

that (IV) $\rightleftharpoons$ (V), with the equilibrium normally much in favour of (IV), provides a satisfactory formulation, which is additionally congruent with extant dipole moment as well as spectrographic evidence.

We are indebted to the Chemical Society for apparatus, to the Commonwealth Research Fund for the award of a Research Studentship (to A. A. H.), and to Dr. Wassermann for (postal) discussions.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, August 20th*, 1948.]

191. *The Polarisation of Aniline dissolved in Benzene.*

By R. J. W. Le Fèvre, (Mrs.) W. P. H. Roberts, and B. M. Smythe.

Disagreement between published sets of data for the dependence upon concentration in benzene of the total polarisation of aniline are probably explained by the shape of the curve, now more fully recorded, relating P_{aniline} with composition.

Emblem and McDowell (*J.*, 1946, 641) have directed attention to certain discrepancies in the literature dealing with the above subject. On consultation of their cited references, together with those of Higasi (*Bull. Inst. Chem. Phys. Res. Tokyo*, 1934, **13**, 1167) and Cowley and Partington (*J.*, 1938, 1598), the situation summarised in Table I is revealed. It does not correspond exactly with the statements of Emblem and McDowell.

Table I.

Source and temp.	Concn. range ($10^5 f_1$).	No. of solutions reported.	Corresponding polarisation range.	Change of P_1 with dilution.
Höjendahl,[1] 25°	5,517	6	74·3	Increase
	41,130 *		68·2	
Hassel & Uhl,[2] 18°	0·6787	3	49·7	Increase
	1·4219 †		48·3 †	
Tiganik,[3] 20°	566·9	4	79·6	Slight
	4,141·1		78·8	increase
Higasi,[4] 25°	2,133	3	79·3	Increase
	8,560 ‡		77·5	
Le Fèvre & Le Fèvre,[5] 25°	2,071·6	3	77·2	Slight
	3,681·5		77·5	decrease
Cowley & Partington,[6] 20°	1,150·5	4	79·5	Slight
	4,460·4		78·6	increase
Emblem & McDowell,[7] 20°	5,190	3	79·4	
	16,040		73·9	Increase

* Calculated from molarities and densities shown in Thesis (*loc. cit.*).
† Molarities and P_{A+O} respectively. ‡ $w_1 \times 10_5$.

References.—(1) Thesis, Copenhagen, 1928; *Physikal. Z.*, 1929, **30**, 391. (2) *Z. physikal. Chem.*, 1929, *B*, **8**, 187. (3) *Ibid.*, 1939, *B*, **14**, 135. (4) *Loc. cit.* (5) *J.*, 1936, 1130. (6) *Loc. cit.* (7) *Loc. cit.*

We have therefore re-studied the aniline–benzene system over a mixture range which is wider than that recorded by any *one* of the above groups of authors separately, and which, in fact, covers them all.

Measurements.—Details of the apparatus, etc., are given by Calderbank and Le Fèvre (*J.*, 1948, 1949), the present data therefore having been obtained with standard- and liquid-containing condensers, a circuit design, and components, which are all different from those previously

Table II.

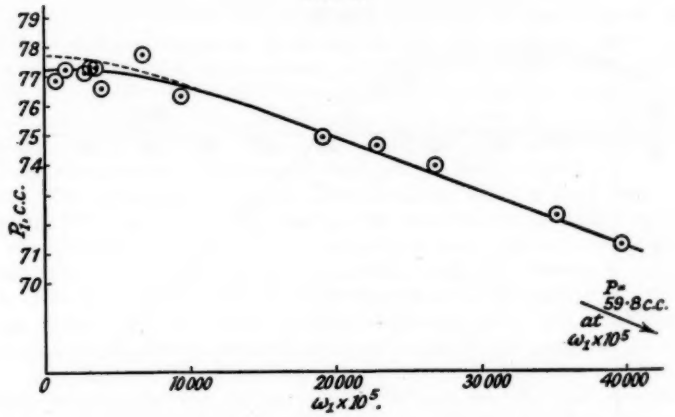
$10^5 f_1$.	$10^5 w_1$.	$\varepsilon^{25°}$.	$a\varepsilon_2$.	$d_4^{25°}$.	βd_2.	P_1 (c.c.).
0	0	2·2725	—	0·87378	—	—
726·97	865·6	2·2978	2·92	0·87493	0·133	76·9
1,202·6	1,430·5	2·3144	2·93	0·87571	0·135	77·3
2,353·3	2,793·2	2·3549	2·95	0·87750	0·133	77·2
2,816·5	3,340·1	2·3716	2·97	0·87825	0·134	77·4
2,942·0	3,488·0	2·3765	2·98	0·87845	0·134	77·5
3,359·7	3,980·2	2·3896	2·94	0·87909	0·134	76·6
5,725·6	6,765·6	2·4762	3·01	0·88280	0·133	77·8
8,035·2	9,434·5	2·5612	3·06	0·88630	0·134	76·4
16,630·8	19,191·0	2·8944	3·24	0·89959	0·136	74·98
19,945·5	22,902·0	3·0355	3·33	0·90499	0·136	74·67
23,626·1	26,945·0	3·1899	3·33	0·91073	0·137	73·98
31,446·6	53,356·0	3·5228	3·54	0·92275	0·1385	72·29
35,676·2	39,750·0	3·7150	3·63	0·92913	0·139	71·34
10^5	10^5	6·68	—	1·017	—	59·8

used by Le Fèvre and Le Fèvre. The aniline was purified by distillation, drying (KOH), and redistillation at 20 mm. ($d_4^{25°}$ 1·017); the benzene by the procedure described in "Dipole Moments" (Methuen, London, 1938, p. 29), wherein also the symbols used in Table II are defined. Concentrations are presented both as molar and weight fractions to simplify comparison with the results of other workers.

The polarisations (last col.) are plotted against concentrations (col. 2) in Fig. 1. It is seen

that at weight fractions greater than *ca.* 0·05, P_{aniline} diminishes with increasing concentration; from $w_1 = 0{\cdot}25$ to $w_1 = 1$ this diminution is nearly rectilinear. Hence we confirm, for the appropriate composition ranges, the *directions* of the changes reported by Höjendahl, Hassel and Uhl, and Emblem and McDowell. The solutions of the remaining authors were dilute, and —in the light of Fig. 1—it is significant that for them the alteration of P_{aniline} with w_1 or f_1 has been much less definite. Since the uncertainties of P_1—evaluated as $M_1[p_2 + (p_{12} - p_2)/w_1]$—can theoretically become hyperbolically greater as w_1 is reduced (cf. Fig. 1 of Müller, *Trans. Faraday Soc.*, 1934, **30**, 729), it is doubtful whether much reliance should be placed on inequalities of a fractional c.c. order drawn from measurements at only 3 or 4 low concentrations. Nevertheless, we note that the data of Le Fèvre and Le Fèvre are satisfactorily superposable on Fig. 1,

FIG. 1.



thus affording, in all, nine solutions at w_1 below 0·05. We suggest, therefore, on present evidence that as the solute concentration approaches zero, P_1 becomes approximately constant. We find, further, that the factors α and β [evaluated from the equations $\varepsilon_{12} = \varepsilon_2(1 + \alpha w_1)$ and $d_{12} = d_2(1 + \beta w_1)$, cf. Le Fèvre and Vine, *J.*, 1937, 1805] are not independent of w_1, but have themselves a straight-line relationship to it. If α and β, extrapolated to $w_1 = 0$, are used to calculate ${}_\infty P_1$, the polarisation (77·7 c.c.) so obtained is closely in the neighbourhood of that given by the direct graphical method (Fig. 1, broken and solid lines).

The matter under discussion scarcely affects the moment in more than the second decimal place. In Table III, we set out the values of μ derived from the polarisations recorded by previous observers when $[R_L]_D = 30{\cdot}6$ is used consistently throughout.

TABLE III.

Summarised results in benzene solution.

Temperature	25°	25°	18°	20°	25°	25°	20°	20°	25°
P_{aniline} at infinite dilution	77·4	77·6	82·6	79·7	80·0	78·4	80·0	81·9	77·7
Moment, μ	1·50	1·51	1·56	1·53	1·54	1·52	1·53	1·56	1·51
Ref. (see Table I and below)	9	1	2	3	4	5	6	7	8

(8) Present work. (9) Estermann (*Z. physikal. Chem.*, 1928, *B*, **1**, 134) used the temperature method on one solution; the above ${}_\infty P_1$ has therefore been calculated by Hedestrand's formula from the mean of Estermann's figures for 20° and 30°. Vassiliev and Sirkin (*Acta Physicochim. U.R.S.S.*, 1941, **14**, 414; read in abstract only) quote μ_{aniline} as 1·54 D., but inaccessibility of experimental details prevents appropriate entries in Tables I and III.

It is noteworthy that from the $\varepsilon^{25°}$ and $d_4^{25°}$ (Table II) of pure aniline, combined with $n_\infty^2 = 2{\cdot}41$—from $[R_L]_\infty = 29{\cdot}2$ (extrapolated from Landolt-Börnstein, "Tabellen")—the moment calculable *via* Onsager's expression (*J. Amer. Chem. Soc.*, 1936, **58**, 1436) for the orientation polarisation, *viz.*,

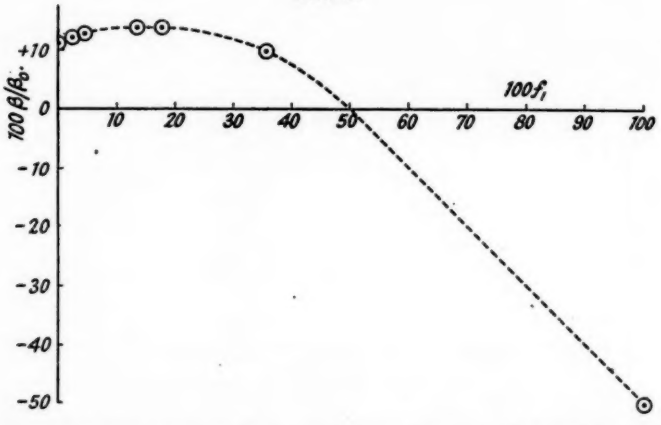
$$_0P_{25°} = (\varepsilon - n_\infty^2)(2\varepsilon + n_\infty^2)M/\varepsilon(n_\infty^2 + 2)^2 d$$

is $0{\cdot}22 \times (47{\cdot}3)^{\frac{1}{2}} = 1{\cdot}51$ D., while if $n^2 = 2{\cdot}51$—from $[R_L]_D = 30{\cdot}6$—μ becomes $0{\cdot}22 \times (44{\cdot}6)^{\frac{1}{2}} = 1{\cdot}47$ D.

Groves and Sugden (*J.*, 1937, 1782) found $(P)_{\text{gas}}$ at 459° K. to be 61·55 c.c. If the same

$[R_L]_D$ is applicable to the gaseous and the liquid state (direct data seem to be lacking), then $(P)^{25°}_{gas} = 30{\cdot}6 + 31 \times 459/298 = 78{\cdot}3$ c.c. There is thus a possibility that the apparent moment of aniline in benzene solution is smaller than the true moment determined as a gas. Such a conclusion would be contrary to the opinions of a number of authors already cited (*e.g.*, Cowley and Partington, Higasi, etc.) who have harmonised the previously supposed fractional nature of the ratio $\mu_{gas}/\mu_{soln.}$ with the recorded *negative* Kerr constant of aniline (Briegleb and Wolf, *Fortschr. Chem.*, 1931, **21**, Part 3, 36; Lippmann, Diss., Dresden, 1912; Schmidt, Diss., Göttingen, 1901). We note, however, that it is only the electric double refraction (E.D.R.) of liquid aniline which is known to be negative; in this state molecular aggregates of some kind, perhaps cybotactates, may reasonably be supposed, the anisotropy of whose polarisability would not be the same as that of the separated molecules. Lippmann (*Z. Elecktrochem.*, 1911,

FIG. 2.



17, 15) records the E.D.R. of mixtures of benzene with aniline: these (Fig. 2) indicate that from $100f_1 = 0$ to about 15, aniline contributes *positively* to the E.D.R. If, therefore, $\mu_{gas}/\mu_{soln.}$ is in fact greater than unity, aniline would merely be taking its place normally with other molecules with positive Kerr constants.

If the association of aniline takes place by hydrogen-bond formation, as infra-red spectroscopic studies have suggested (Gordy, *J. Chem. Physics*, 1939, **7**, 163; Buswell, Downing, and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2759), the dimer will have some stereo-resemblance (the N–H–N arrangement being assumed rectilinear) to, *e.g.*, hydrazobenzene, the contribution of which to the E.D.R. of benzene is *negative* even at 0·9 mol. % (Lippmann, *loc. cit.*).

Finally, it is of interest that for many other properties, benzene–aniline mixtures seem to obey a normal additive law notwithstanding the fact that the apparent molecular weight of aniline in benzene is stated to rise with increasing concentration (Udovenko and Usanovitsch, *J. Gen. Chem. Russia*, 1940, **10**, 17).

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UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, August 25th*, 1948.]

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192. *The Constitution of Yeast Ribonucleic Acid. Part XIV. The Preparation and Structures of the Pyrimidine Nucleotides.*

By G. R. BARKER, (the late) J. MASSON GULLAND, H. SMITH, and J. F. THOMAS.

An improved routine laboratory preparation of cytidine-3′ phosphate and uridine-3′ phosphate from yeast ribonucleic acid is described, the latter being isolated as its crystalline *disodium* salt. It is shown that the same pyrimidine nucleotides are obtained whether the fission of the polynucleotide is carried out in alkaline or acid medium.

A SURVEY of the older literature reveals a number of methods for preparing nucleotides from yeast ribonucleic acid (for references see Levene and Bass, " Nucleic Acids ", Chem. Cat. Co.,

New York, 1931; Gulland, *J.*, 1938, 1722; Lythgoe, *Ann. Reports*, 1944, 200), in which fission of the polynucleotide is brought about by enzymes or in acid or alkaline medium. None of the processes so far described, however, results in nucleotides in such yields as to warrant the assumption that they are the sole hydrolytic products. It was desirable, therefore, to attempt to devise methods whereby nucleotides could be obtained in higher and more reproducible yields, and this paper describes a process for the preparation of pyrimidine nucleotides which has proved technically more convenient and more consistent than those described in the literature.

After the completion of this work, a new method for the preparation of cytidylic acid and diammonium uridylate was reported by Loring, Roll, and Pierce (*J. Biol. Chem.*, 1948, **164**, 729), but the yields of cytidylic acid recorded by these authors are slightly less than we have obtained by the present procedure. The yield of diammonium uridylate obtained by the American workers is roughly comparable with that of disodium uridylate which we obtain. We find, however, that conversion of brucine uridylate into the disodium salt is much more satisfactory than the isolation of the nucleotide as its diammonium salt. Furthermore, the disodium salt is of greater use in the biological experiments for which the present investigations were undertaken. However, the yields of pyrimidine nucleotides obtained by Loring *et al.* and by us do not preclude the possibility that compounds other than 3′-phospho-pyrimidine nucleosides are formed during the fission of yeast ribonucleic acid, and this problem together with the analogous one regarding purine nucleotides will form the subject of another paper.

The separation of uridylic and cytidylic acids from a mixture of four nucleotides is a tedious and lengthy process. The use of an acid medium for the hydrolysis of the nucleic acid, however, simplifies to a large extent the subsequent operations since purine nucleotides are destroyed under these conditions. The process now described uses this means of splitting the nucleic acid and is a modification of the method of Bredereck and Richter (*Ber.*, 1938, **71**, 718), who hydrolysed yeast nucleic acid with boiling dilute sulphuric acid, and, after removal of guanine and of sulphate ions, precipitated cytidylic acid with anhydrous pyridine, in which the uridylic acid dissolved. The innovations which we have introduced into this method greatly increase the ease of manipulation and the reproducibility of the results, and overcome many of the difficulties experienced by previous workers (see Loring, Roll, and Pierce, *loc. cit.*). The most important improvements are (*a*) removal of phosphate ions together with sulphate ions, which avoids contamination of the uridylic acid with phosphoric acid and results in more consistent yields of this nucleotide; (*b*) improvement of the technique for the precipitation of cytidylic acid in such a way that it is obtained initially in a granular filtrable condition instead of as a gum; and (*c*) the isolation of uridylic acid as its crystalline *disodium* salt.

Although acid hydrolysis of pentose nucleic acids has been used for a considerable time in the preparation of pyrimidine nucleotides, no adequate comparison has been made of the materials obtained by this method and those isolated after alkaline hydrolysis. It is known that the uridylic acid obtained by acid hydrolysis of yeast nucleic acid by the method now described is uridine-3′ phosphate (Gulland and Smith, *J.*, 1947, 338). Since, however, the nature of the internucleotide linkages in the polynucleotide molecule is unknown, it cannot be predicted whether or not the same linkages are broken under acid and alkaline conditions, and it cannot, therefore, be assumed that identical nucleotides are produced in each case. In fact, there is evidence (Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611) that certain phosphoric esters behave differently in acid and alkaline hydrolytic fission. Yeast nucleic acid was therefore hydrolysed with cold dilute aqueous sodium hydroxide, and, after removal of the purine nucleotides by the methods of Buell and Perkins (*J. Biol. Chem.*, 1927, **72**, 21) and Steudel and Peiser (*Z. physiol. Chem.*, 1923, **127**, 262) and finally by acid hydrolysis, the pyrimidine nucleotides were separated with pyridine. In this way, cytidylic acid, disodium uridylate, and dibrucine uridylate were obtained, identical with the compounds obtained after degradation of the polynucleotide with acid. Furthermore, the same uridylic acid was obtained by deamination of cytidylic acid, obtained by acid hydrolysis, by the method of Bredereck (*Z. physiol. Chem.*, 1934, **224**, 79). It follows, therefore, that uridine-3′ phosphate and cytidine-3′ phosphate are produced from yeast ribonucleic acid, whether fission of the internucleotide linkages is carried out in acid or alkaline medium. Conversely, it may be that the unknown internucleotide linkage which is labile towards alkali is also labile towards acid, and that the stabilising effect of the pyrimidine bases on the phosphoric ester grouping at position 3′ does not operate in the case of this unknown linkage. This point can only become clear when a complete knowledge of the hydrolytic products of the polynucleotide is achieved.

Experimental.

Preparation of Cytidylic and Uridylic Acids by Acid Hydrolysis.—Yeast ribonucleic acid (Pharmco-Chemical Products Ltd.) (400 g.) was added, with stirring, to hot 2% w/v sulphuric acid (4 l.), and the solution was refluxed for 2 hours. After standing overnight, the mixture was made 3·8% w/v with respect to sulphuric acid and left for several days. Guanine sulphate was removed by filtration, and hot saturated barium hydroxide solution was added to the filtrate until the solution was alkaline to phenolphthalein. The precipitate of barium phosphate and barium sulphate was collected by centrifugation and washed 6 times by resuspension in boiling water (2 l. each) and centrifugation. The combined centrifugates were freed from barium ions quantitatively by addition of sulphuric acid and filtration, and the filtrate was concentrated under reduced pressure to a thick syrup, freedom from barium and sulphate ions being checked during the evaporation of a more concentrated solution. The thick syrup was poured into anhydrous pyridine (3 l.) which had been cooled below 0° in a freezing mixture, and the pyridine cytidylate which was formed on kneading the gum was left in the freezing mixture for 3 hours and then collected by filtration and washed with ice-cold pyridine (500 c.c.). The combined filtrate and washings were evaporated under reduced pressure to a thick syrup, and the pyridine treatment repeated. The filtrate and washings were evaporated as before, and a portion of the syrup tested with pyridine. Usually the precipitation of pyridine cytidylate was complete at this stage, but the above procedure was repeated if necessary. The combined granular precipitates constituted the cytidylic acid fraction, the filtrates from which were concentrated under reduced pressure to a syrup (uridylic fraction).

Cytidylic Fraction.—The pyridine cytidylate was dissolved in water (2 l.) and evaporated to a syrup under reduced pressure to remove uncombined pyridine. The residue was dissolved in water (1·5 l.), and lead cytidylate precipitated by addition of 25% solution of lead acetate (about 400 c.c.), the pH of the solution being kept at 7·2 by addition of ammonia solution (*d* 0·88) (about 25 c.c.) until precipitation was complete. The lead salt was collected by centrifugation and washed 4 times by stirring vigorously with water (2 l.) followed by centrifugation. Passage of hydrogen sulphide for 5 hours through a stirred suspension of the lead salt in water (3 l.) formed a solution of the free acid. The mixture was heated to 80°, passage of hydrogen sulphide being continued, and the coagulated lead sulphide was removed by filtration (charcoal), washed with hot water, and resuspended in water (3 l.). The mixture was saturated with hydrogen sulphide, and, with hydrogen sulphide passing through the solution, the temperature was raised to 80° for 1 hour. The lead sulphide was again removed by filtration, and washed with hot water. The combined filtrates and washings were aerated to remove excess of hydrogen sulphide and concentrated under reduced pressure to 400—500 c.c., and the solution was boiled with charcoal and filtered. To the boiling filtrate, boiling absolute industrial alcohol (about 600 c.c.) was added until an incipient turbidity was produced. On seeding, crystals of cytidylic acid separated immediately in needles, which, after being kept in the refrigerator for several days, were collected (23 g.) and dried in a vacuum over phosphoric oxide. The material was recrystallised from boiling water (25 parts) by addition of boiling absolute industrial alcohol (about 25 parts) (Found in the anhydrous material: C, 33·4; H, 4·4; N, 12·7; P, 9·4. Calc. for $C_9H_{14}O_8N_3P$: C, 33·4; H, 4·3; N, 13·0; P, 9·6%). In a 1 mm. tube in a bath at 220°, the temperature rise being 5° per minute, the needles melted at 231—233° (vigorous decomp.). In water the material dried as for analysis showed $[\alpha]_D^{25°}$ +36·7° (*c*, 2·2). In 2% aqueous sodium hydroxide the material dried as for analysis had $[\alpha]_D^{25°}$ +22·7 (*c*, 1·1).

Uridylic Fraction.—The pyridine uridylate was converted into the free nucleotide as described for cytidylic acid. The filtrates and washings from the lead sulphide were freed from hydrogen sulphide by aeration, and evaporated under reduced pressure to 200 c.c. A small quantity was titrated with sodium hydroxide solution, using phenolphthalein, and brucine (5% in excess of that theoretically required to form dibrucine uridylate) dissolved in alcohol (100 c.c.) was added to the bulk of the solution. On stirring and seeding, brucine uridylate crystallised, and, after being kept overnight in the refrigerator, was collected by filtration. After being recrystallised twice from 33% alcohol (80 parts) in the presence of charcoal it had m. p. 185—195° under the standard conditions given by Gulland and Smith (*loc. cit.*) (yield 63 g.) [Found in anhydrous material: C, 59·1; H, 6·1; N, 7·6; P, 2·8. Calc. for $C_9H_{13}O_9N_2P,(C_{23}H_{26}O_4N_2)_2$: C, 59·3; H, 5·9; N, 7·6; P, 2·8%]. Sufficient N-sodium hydroxide solution was added to a well-stirred suspension of the brucine salt in boiling water (600 c.c.) in order to convert all of it into the disodium salt. After the mixture had been allowed to cool and left overnight, the bulk of the brucine was filtered off and washed with water, and the remainder removed from the filtrate and washings by extraction with chloroform. The solution of *disodium uridylate* was evaporated to 50 c.c., filtered through charcoal, and cooled in ice. Absolute industrial alcohol was added very slowly with mechanical stirring until a turbidity was first formed. The solution was then seeded, and the addition of alcohol was continued periodically, with stirring, until complete crystallisation had occurred (about 500 c.c.). After the mixture had been kept in the refrigerator overnight, the needles (18 g.) were collected at the pump. They were recrystallised by dissolving them in hot water (25 c.c.), filtering the solution in the presence of charcoal, cooling in ice, seeding, and adding absolute industrial alcohol very slowly (about 250 c.c.) as before (Found in the anhydrous material: C, 29·8; H, 3·2; N, 7·5; P, 8·4. $C_9H_{11}O_9N_2PNa_2$ requires C, 29·4; H, 3·2; N, 7·6; P, 8·4%). Loss in weight on drying, 19·3; the tetrahydrate requires 19·6%. The anhydrous material had in water $[\alpha]_D^{25°}$ +19·8° (*c*, 2·25). The sodium salt was dissolved in water and the rate of dephosphorylation by N/10-sulphuric acid at 100° was carried out under the same conditions as those described by Gulland and Smith (*loc. cit.*), with the following results (0·48 mg. of P per 10 c.c. of solution):

Hours	1	3	5	10	22	24
Dephosphorylation, %	8	17	28	45	71	77

Cytidylic acid (11 g.) was deaminated as described by Bredereck (*loc. cit.*), and after purification through the brucine salt, sodium uridylate (4·4 g.) was obtained as described above. The anhydrous material had in water $[\alpha]_D^{24°}$ +21·4° (*c*, 1·0).

Preparation of Uridylic and Cytidylic Acids by Alkaline Hydrolysis.—Yeast ribonucleic acid (Pharmco-Chemical Products Ltd.) (200 g.) was hydrolysed by 5 l. of 1% sodium hydroxide solution at room temperature for 3 days. Guanylic acid was removed as its ammonium salt by the method of Buell and Perkins (*loc. cit.*), and adenylic acid crystallised directly as described by Steudel and Peiser (*loc. cit.*). The mother liquors from the crystallisations of the adenylic acid were combined, and after hydrolysis at 100° in 2% w/v sulphuric acid (2 l.) for 2 hours, cytidylic and uridylic acids were isolated as described above for the acid hydrolysate. The following were obtained :

Cytidylic acid (4 g.), which, when placed in a 1 mm. tube in a bath at 220° the temperature rise being 5° per minute, melted at 231—233° (vigorous decomp.); when mixed with a sample of cytidylic acid prepared by acid hydrolysis it had m. p. 231—233° under the same conditions; in water, the material dried as for analysis had $[\alpha]_D^{25°}$ +37·0° (*c*, 2·2); in 2% sodium hydroxide solution it had $[\alpha]_D^{25°}$ +21·8° (*c*, 1·1).

Dibrucine uridylate (6 g.), m. p. and mixed m. p. with sample of brucine uridylate prepared by acid hydrolysis of the nucleic acid 185—195° under the standard conditions given by Gulland and Smith (*loc. cit.*).

Disodium uridylate (1·6 g.), which (anhydrous material) had in water $[\alpha]_D^{26°}$ +20·0° (*c*, 2·64); it was dissolved in water, and the rate of dephosphorylation by N/10-sulphuric acid at 100° was carried out under the same conditions as those described by Gulland and Smith (*loc. cit.*), with the following results (0·48 mg. of P per 10 c.c. of solution) :

Hours	1	3	5	10	22	24
Dephosphorylation, %	6	19	27	42	68	73

It is a pleasure to record our gratitude to the British Empire Cancer Campaign for financial assistance. Our thanks are due to Mr. J. E. Still for microanalyses.

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193. *The Reactions of Some Cyclic Tertiary Amines with N-Halogeno-compounds.*

By S. L. COSGROVE and WILLIAM A. WATERS.

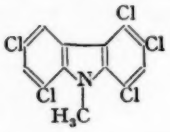
A number of cyclic tertiary amines have been chlorinated with *N* : 2′ : 4′ : 6′-tetrachloro-benzanilide and brominated with *N*-bromosuccinimide. Dealkylation occurs to a slight extent, but in general the halogenation is facile, extensive, and not selective with regard to position in the molecule. Often it is accompanied by dehydrogenation to a ring system of aromatic type. This accords with the view that the *N*-halogeno-compounds exhibit chemical reactivities of homolytic type.

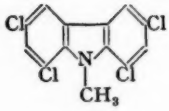
THE discovery by Crane, Forrest, Stephenson, and Waters (*J.*, 1946, 827) that tertiary aliphatic amines, such as methyldi-(2-chloroethyl)amine, could be dealkylated upon chlorination with substituted *N*-chlorobenzanilides in a non-ionising solvent seemed to us to offer a new route for the controlled degradation of cyclic amines such as *N*-methylpiperidine, nicotine, and other alkaloids, but the following work shows that this method of degradation of amines is of little practical value.

Although a certain amount of dealkylation occurs when the cyclic *N*-methylamines, *N*-methylpiperidine, *N* : 6 : 8-trimethyl-1 : 2 : 3 : 4-tetrahydroquinoline, nicotine, narcotine, and ergotoxine are treated with *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide in cold carbon tetrachloride or benzene solutions, the amount of formaldehyde which is liberated corresponds to only 1—2% of the *N*-methyl content of the amine taken. Furthermore, even in the simplest cases we were unable to establish the production of the corresponding demethylated secondary cyclic amine (*e.g.*, piperidine), or of any of the amino-aldehydes which could have been formed by the rupture of the heterocyclic ring at a N–C link. Similarly, *N*-benzylpiperidine gave only a very small yield of benzaldehyde, though dimethylaniline was extensively demethylated. Even when one or two molecular equivalents of *N*-chloro-imide were employed the reaction produced much hydrogen chloride, and an examination of the basic material in the reaction product always showed that a small part of the amine had been extensively chlorinated, though the majority of it could be recovered unchanged. From the large amount of active chlorine which could be taken up it appeared that the saturated ring system of *N*-methylpiperidine and its analogues had suffered chlorination in all possible positions, and that the chlorinated reaction product then lost hydrogen chloride very easily, possibly to yield bases of the pyridine type, traces of which could indeed be detected by smell.

Attention was then directed to the chlorination of *N*-methyltetrahydrocarbazole, in which chlorination in an allyl position was envisaged as a possibility (compare Ziegler *et al.*, *Annalen*,

1942, **551**, 80). With this substance we were able to establish that, in benzene solution, nuclear substitution and elimination of hydrogen chloride from the aliphatic ring proceeded simultaneously since a pentachloro-*N*-methylcarbazole (possibly I) was isolated as a reaction product. Under the most drastic conditions, *N*-methylcarbazole yielded only a tetrachloro-derivative (probably II), so that the extra chlorine atom of (I) must have been introduced into the *cyclo*hexene ring of the starting product before dehydrogenation to the benzenoid ring was complete. In support of this view of the reaction, we then found that *N*-methyldihydroacridine gave acridine methochloride, evidently by substitution at the central methylene group followed by elimination of hydrogen chloride.

(I.) 

 (II.)

N-Bromosuccinimide reacted throughout in a very similar manner. Thus in carbon tetrachloride suspension *N*-methylpiperidine yielded a little formaldehyde, *N*-benzylpiperidine gave a little benzaldehyde, and dimethylaniline gave some formaldehyde. Just as triethylamine gives acetaldehyde, glyoxal, and diethylamine on chlorination with *N*-chloro-imides (Waters *et al.*, *loc. cit.*), so these same products were identified as resulting from the reaction between triethylamine and *N*-bromosuccinimide in carbon tetrachloride suspension. The bromination of *N*-methyltetrahydrocarbazole does not proceed well except in the presence of a little benzoyl peroxide (compare Schmidt and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573; Schmidt and Leutersegger, *ibid.*, 1947, **30**, 1965), and appears to give at most a tetrabromo-*N*-methylcarbazole, whilst *N*-methylcarbazole gives no more than a tribromo-compound: A corresponding dehydrogenation of an alicyclic ring system by *N*-bromosuccinimide has recently been noted by Barnes (*J. Amer. Chem. Soc.*, 1948, **70**, 145). Bromine reacts quite differently with these tertiary amines: it first forms red perbromides, and does not effect any detectable dealkylation.

The foregoing reactions of the *N*-chloro- and *N*-bromo-compounds accord with the hypothesis of substitution *via* homolytic bond fission (compare Robertson and Waters, *J.*, 1947, 492) since this would not be expected to be noticeably selective with respect to the attack on any one particular C–H bond.

In contrast to the saturated amines which have already been mentioned, pyridine, α-picoline, and quinoline were not substituted either by *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide or by *N*-bromosuccinimide, though they promoted a slight evolution of free chlorine from the *N*-chloro-imide in boiling dry carbon tetrachloride solution. Evidently the methyl group of α-picoline does not show marked allylic reactivity.

Experimental.

Reaction between N-*Methylpiperidine and* N : 2′ : 4′ : 6′-*Tetrachlorobenzanilide in Benzene.*—*N*-Methylpiperidine (8·6 ml.) in dry benzene (100 ml.) was slowly treated, with mechanical stirring, with 24 g. (1 equiv.) of the chloro-imide in 75 ml. of benzene, the mixture being kept cool with iced water. On the following day 50 ml. of dilute hydrochloric acid were added, solid trichlorobenzanilide was removed by filtration, and the two liquid layers were separated. The benzene layer contained only a little trichlorobenzanilide, whilst the aqueous layer yielded, on distillation, a little formaldehyde, which was characterised as its dimedone derivative, m. p. and mixed m. p. 191°. On neutralisation *N*-methylpiperidine was recovered from the aqueous layer in about 50% yield: besides this there was only a small dark residue from which positive tests for secondary bases could not be obtained. When excess of *N*-chloro-imide was used this dark residue smelt distinctly of pyridine, but this, if present, was insufficient in quantity for definite characterisation. A quantitative experiment indicated that the yield of formaldehyde was about 1 mol. per 80 mols. of tertiary base.

The chlorination proceeded similarly in dry carbon tetrachloride solution, but it was found that, on long standing, *N*-methylpiperidine reacted with carbon tetrachloride with deposition of *N*-methylpiperidine hydrochloride.

N-Benzylpiperidine (Wallach, *Annalen*, 1905, **343**, 74) reacted with the *N*-chloro-imide in a similar way, but gave no characterisable reaction products, other than a very small percentage of benzaldehyde. The following figures illustrate the outcome of the chlorination in benzene at 18°:

Base taken, mol.	0·01	0·01	0·01	0·005
Chloro-imide taken, mol.	0·01	0·02	0·03	0·035
Chloro-imide reacted, %	98·6	99·7	99·8	86·9
Chlorine converted into Cl^-, %	30·5	29·9	27·2	14·1

This indicates that there is extensive chlorination of a small fraction of the original base.

N : 6 : 8-*Trimethyl*-1 : 2 : 3 : 4-*tetrahydroquinoline* was prepared in the hope that it might give more

recognisable basic products after chlorination in a similar manner, but again the only product which could definitely be characterised was formaldehyde. This base, m. p. 48·5°, b. p. 127°/16 mm., was prepared by methylating 6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (Ewins, *J.*, 1913, **103**, 102) with formaldehyde and formic acid (compare *J. Amer. Chem. Soc.*, 1933, **55**, 5476) (Found : C, 81·6; H, 9·7; N, 8·1. $C_{12}H_{17}N$ requires C, 82·3; H, 9·7; N, 8·0%). Its *picrate* had m. p. 143° (Found : C, 53·4; H, 5·06. $C_{18}H_{20}O_7N_4$ requires C, 53·5; H, 4·95%).

The alkaloids nicotine, narcotine, and ergotoxine were also chlorinated by the *N*-chloro-imide in benzene solution. Each yielded a small quantity of formaldehyde, owing to fission of the molecule at an *N*-methyl group. Dimethylaniline gave formaldehyde (weighed as its dimedone derivative) corresponding to 1 CH_2O per 1·6 NMe_2 groups (*i.e.*, very much more than from the saturated heterocyclic compounds).

Brominations with N-*Bromosuccinimide.*—1·94 G. of *N*-methylpiperidine in 25 ml. of dry chloroform were mixed with 10·5 g. (3 equivs.) of *N*-bromosuccinimide in the same solvent. Rapid reaction set in after 1 minute, but was controlled by cooling in ice-water. After 12 hours water was added, and after filtration the two liquid layers were separated. The aqueous layer, on distillation, yielded a little formaldehyde (dimedone derivative separated), but no sign of a salt of a secondary base. No other derivatives of the original base, except its hydrobromide, could be isolated from the remaining portions of the reaction mixture.

The quantitative bromination of *N*-benzylpiperidine in carbon tetrachloride gave the following results, indicating again the extensive bromination of a small fraction of the base :

Base taken, mol.	0·0063	0·0063	0·0063
Bromo-imide taken, mol.	0·0059	0·0118	0·0177
Bromo-imide reacted, %	99·3	99·3	99·2
Bromine converted into Br^-, %	51·7	39·3	18·6

Benzaldehyde and *N*-benzylpiperidine (separated as the picrate) were the only identifiable reaction products.

N-Bromosuccinimide under carbon tetrachloride reacted with dimethylaniline slowly, after an induction period of several minutes, and gave an appreciable percentage of formaldehyde. The *N*-bromo-imide reacted immediately with triethylamine in dry carbon tetrachloride and gave a red gum. This was treated with dilute hydrochloric acid, and the aqueous solution was separated. It gave a positive colour reaction for acetaldehyde with sodium nitroprusside and piperidine; when treated with dimedone it yielded the anhydride of the glyoxal derivative (m. p. 215°, *ex* alcohol) and with 2 : 4-dinitrophenylhydrazine the derivatives of both acetaldehyde (m. p. 155°) and glyoxal (m. p. 327°). From this aqueous solution there were also obtained both unchanged triethylamine (as the picrate) and diethylamine (as the toluene-*p*-sulphonamide, m. p. and mixed m. p. 60°).

N-Bromosuccinimide did not react with either pyridine or α-picoline in dry carbon tetrachloride solution. When each of these bases was refluxed with *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide in dry benzene solution a small amount of free chlorine was slowly evolved, even when precautions were taken to maintain anhydrous conditions by passing a slow current of thoroughly dried air through the boiling solutions. No chlorination of either base could be detected however.

N-Methylpiperidine in dry carbon tetrachloride reacted immediately with bromine in the same solvent to give a deep red solution and eventually a red gum. This gum proved to be a perbromide, readily converted into *N*-methylpiperidine hydrobromide, but after decomposition with water the product gave no aldehydic reactions, and no tests for secondary bases.

Halogenation of N-*Methyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole.*—(*a*) 3·7 G. of base (Plant and Perkin, *J.*, 1921, **119**, 1831) and 47 g. (7 equivs.) of *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide were allowed to react in 130 ml. of dry benzene. The mixture became warm and evolved hydrogen chloride. After 6 hours, 50 ml. of water were added, solid trichlorobenzanilide was filtered off, and the liquid layers were separated. The aqueous layer on treatment with dimedone yielded only 1 mg. of the formaldehyde derivative, m. p. 191°. The benzene layer on evaporation gave a brown paste, from which by repeated crystallisation from alcohol there was obtained a *pentachloro*-N-*methylcarbazole* (possibly I), m. p. 196·5° (Found : C, 44·0; H, 1·48; C, 50·9. $C_{13}H_6NCl_5$ requires C, 44·2; H, 1·7; Cl, 50·2%). This showed a very weak violet fluorescence in ultra-violet light, with a weak afterglow. Dehalogenation could not be effected by heating either with magnesium turnings in dry ether or with amalgamated zinc in hydrochloric acid.

(*b*) 3·7 G. of base and 25 g. (7 equivs.) of *N*-bromosuccinimide were suspended in 100 ml. of dry carbon tetrachloride. Reaction set in, with evolution of hydrogen bromide after an induction period of 5 minutes. After 48 hours water was added, and the layers were separated as in (*a*). The carbon tetrachloride layer yielded a brown solid which by repeated crystallisation, using alternately ethanol and light petroleum, gave a microcrystalline *tetrabromo*-N-*methylcarbazole*, m. p. 85° (Found : C, 30·4; H, 1·99; Br, 63·9. $C_{13}H_7NBr_4$ requires C, 31·3; H, 1·4; Br, 63·9%).

Halogenation of N-*Methylcarbazole.*—(*a*) 3 G. of base (compare Ehrenreich, *Monatsh.*, 1911, **32**, 1104) and 28 g. (5 equivs.) of chloro-imide were mixed in 80 ml. of dry benzene. There was no rapid reaction, but trichlorobenzanilide slowly separated. After 12 hours water was added and the liquid layers were separated. The aqueous portion gave no aldehydic reactions. The benzene layer yielded, after repeated crystallisations from ethanol, a *tetrachloro*-N-*methylcarbazole* (possibly II), m. p. 161° (Found : C, 49·1; H, 2·10; Cl, 44·8. $C_{13}H_7NCl_4$ requires C, 48·9; H, 2·19; Cl, 44·5%), together with a less pure *trichloro*-N-*methylcarbazole*, m. p. 113° (Found : Cl, 39·1. $C_{13}H_8NCl_3$ requires Cl, 37·4%), which on further treatment with the *N*-chloro-imide in benzene yielded the tetrachloro-*N*-methylcarbazole of m. p. 161°. When the latter was kept with excess of *N*-chloro-imide no further chlorination occurred, and the initial material could be recovered unchanged.

(*b*) 2 G. of base, 7·9 g. (4 equivs.) of *N*-bromosuccinimide, and 0·2 g. of benzoyl peroxide were refluxed together in 40 ml. of dry carbon tetrachloride. The liquid portion of the product left a green gummy

residue on evaporation, from which by repeated crystallisation from alcohol there were obtained a *tribromo-N-methylcarbazole*, m. p. 186° (Found: C, 37·7; H, 2·0; Br, 56·1. $C_{13}H_8NBr_3$ requires C, 37·9; H, 1·9; Br, 57·4%), and a less pure *dibromo-N-methylcarbazole*, m. p. 141° (Found: Br, 51·8. $C_{13}H_9NBr_2$ requires Br, 47·2%).

Chlorination of N-*Methyl*-9 : 10-*dihydroacridine*.—1 G. of base (Decker and Dunant, *Ber.*, 1906, **39**, 2721) in 10 ml. of dry benzene was treated with 3·44 g. (2 equivs.) of the *N*-chloro-imide in 20 ml. of benzene and reacted immediately. After 24 hours the yellow solid was filtered off and extracted four times with hot dilute hydrochloric acid, and this extract was evaporated on the water-bath. It left a yellow residue with a strong green fluorescence in alcoholic solution, and, when treated with alcoholic sodium picrate, yielded the picrate of *N*-methylacridine, m. p. 186° (Found: C, 56·1; H, 3·3; N, 12·5. Calc. for $C_{20}H_{15}O_7N_4$: C, 56·9; H, 3·3; N, 13·3%). For confirmation, the same product was prepared by methylating acridine with methyl sulphate and converting the product into its picrate.

The non-basic residue from the chlorination reaction was warmed with alkali and then recrystallised from alcohol. It gave *N*-methylacridone, m. p. and mixed m. p. 202°. There was no experimental evidence of the production of formaldehyde.

The analyses were carried out microchemically by Drs. Weiler and Strauss. All m. p.s are corrected.

DYSON PERRINS LABORATORY, OXFORD. [*Received, September 16th*, 1948.]

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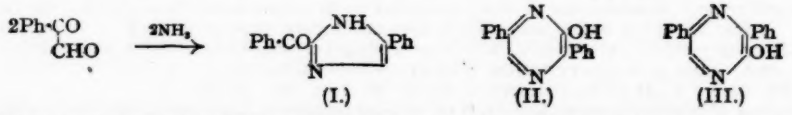
194. *Pyrazine Derivatives. Part IX. The Conversion of* DL-*Phenylglycine Anhydride into* 3-*Hydroxy*-2 : 5-*diphenylpyrazine.*

By J. J. GALLAGHER, G. T. NEWBOLD, F. S. SPRING, and J. C. WOODS.

Treatment of DL-phenylglycine anhydride with phosphoryl chloride gives a mixture from which 3-hydroxy-2 : 5-diphenylpyrazine (II) and 3 : 6-dichloro-2 : 5-diphenylpyrazine have been isolated. 3-Hydroxy-2 : 5-diphenylpyrazine has also been obtained in good yield (*a*), together with the isomeric 2-benzoyl-4(5)-phenylglyoxaline (I), by treatment of phenylglyoxal with ammonium formate and (*b*) by the action of nitrous acid upon 3-amino-2 : 5-diphenylpyrazine.

THE limitations of the methods which are available for the synthesis of 3-hydroxy-2 : 5-dialkylpyrazines have been discussed by Baxter, Newbold, and Spring (*J.*, 1947, 370), and a variety of new methods have been described in earlier Parts of this series (*J.*, 1947, 370, 1179, 1183; 1948, 1855, 1862; this vol., p. 300). In a general study of antibacterial compounds, isolated from *Aspergillus flavus* and other micro-organisms, it became necessary to extend these methods to the synthesis of 3-hydroxy-2 : 5-diarylpyrazines and, in the first place, we have limited this study to the preparation of 3-hydroxy-2 : 5-diphenylpyrazine. The literature concerning this compound is very confused. By the action of ammonia on phenylglyoxal, Pinner (*Ber.*, 1905, **38**, 1531) obtained two isomeric products, $C_{16}H_{12}ON_2$, m. p.s 202° and 280°. The latter was considered to be 2-benzoyl-4(5)-phenylglyoxaline (I) and the former 3-hydroxy-2 : 5-diphenylpyrazine (II). The lower-melting isomer (cf. Müller and Pechmann, *Ber.*, 1889, **22**, 2556; Pinner, *Ber.*, 1902, **35**, 4131) was shown to be identical with a compound obtained by Engler and Hassenkamp (*Ber.*, 1885, **18**, 2240) by the action of ammonia upon ω-dibromoacetophenone. It had also been obtained previously by Japp and Miller (*J.*, 1887, 29), by treatment of benzil with hydrogen cyanide, and by Minovici (*Ber.*, 1899, **32**, 2206), by the action of hydrogen chloride on mandelonitrile, and was likewise formulated by Japp and Knox (*J.*, 1905, 701) as 2-keto-3 : 6-diphenyl-1 : 2-dihydropyrazine (equivalent to 3-hydroxy-2 : 5-diphenylpyrazine).

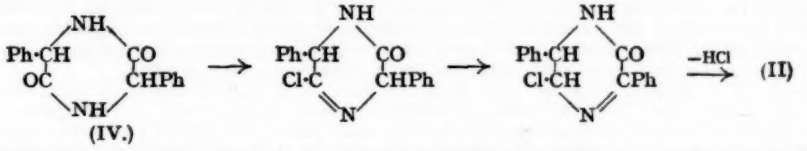


(I.) (II.) (III.)

Gastaldi (*Gazzetta*, 1921, **51**, 233) obtained 3-hydroxy-2 : 5-diphenylpyrazine, m. p. 284°, by a route involving reaction of the hydrogen sulphite derivative of oximinoacetophenone with potassium cyanide followed by treatment of the mixture with hydrochloric acid, whereupon a product, formulated as 3 : 6-dicyano-2 : 5-diphenylpyrazine, was obtained. Alkaline hydrolysis of this gave 3-hydroxy-2 : 5-diphenylpyrazine-6-carboxylic acid, decarboxylation of which yielded 3-hydroxy-2 : 5-diphenylpyrazine, m. p. 284°, identical with the compound described by Pinner as 2-benzoyl-4(5)-phenylglyoxaline. Gastaldi's argument is dependent upon the structure of the intermediate dicyanide formulated by him as 3 : 6-dicyano-2 : 5-diphenylpyrazine; this structure has been supported by Sharp and Spring (*J.*, 1948, 1862) by the

synthesis of 3 : 6-dicyano-2 : 5-dimethylpyrazine by an alternative method starting from ethyl 2 : 5-dimethylpyrazine-3 : 6-dicarboxylate, the product proving to be identical with the dicyanide obtained from oximinoacetone by Gastaldi's method.

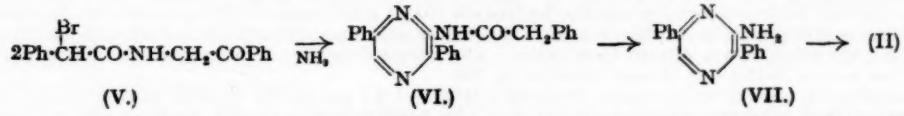
An unambiguous synthesis of 3-hydroxy-2 : 5-diphenylpyrazine from DL-phenylglycine anhydride (3 : 6-diketo-2 : 5-diphenylpiperazine) (IV) has now been effected. Treatment of the anhydride with phosphoryl chloride gives a mixture of 3-hydroxy-2 : 5-diphenylpyrazine (II), m. p. 285°, and 3 : 6-*dichloro*-2 : 5-*diphenylpyrazine*. This is the first example, within our experience, of the direct conversion of a diketopiperazine into a hydroxypyrazine, and it is presumably to be attributed to the ready loss of the elements of hydrogen chloride from an intermediate monochloro-dihydropyrazine derivative, thus :



The diketopiperazines which have been previously similarly treated give mixtures of 3-chloro- and 3 : 6-dichloro-2 : 5-disubstituted pyrazines (Baxter and Spring, *J.*, 1947, 1179), whereas in the case of phenylglycine anhydride the corresponding 3-chloro-2 : 5-diphenylpyrazine was not isolated. However, the latter may well be a product since the resinous material remaining after the isolation of the dichloro-compound gave a further quantity of 3-hydroxy-2 : 5-diphenylpyrazine when heated with potassium hydroxide.

The 3-hydroxy-2 : 5-diphenylpyrazine obtained by the use of this method is identical with the compound described by Gastaldi and also with the higher-melting product obtained by the action of ammonia upon phenylglyoxal (or better by the action of ammonium formate upon phenylglyoxal). The isomeric lower-melting compound, m. p. 197—198°, obtained from the latter reaction, may be either 2-benzoyl-4(5)-phenylglyoxaline (I) or 2-hydroxy-3 : 5-diphenylpyrazine (III).

An attempt to synthesise the latter for comparison purposes was unsuccessful since reaction of ammonia with ω-bromophenylacetamidoacetophenone (V) gave 3-phenylacetamido-2 : 5-



diphenylpyrazine (VI) and not the expected 2-hydroxy-3 : 5-diphenylpyrazine (Newbold, Spring, and Sweeny, this vol., p. 300). This reaction, however, led to an independent synthesis of 3-hydroxy-2 : 5-diphenylpyrazine in which 3-amino-2 : 5-diphenylpyrazine (VII), obtained from (VI) by alkaline hydrolysis, is treated with nitrous acid. 3-Amino-2 : 5-diphenylpyrazine could not be obtained by the action of sodamide upon 2 : 5-diphenylpyrazine.

Although we have not succeeded in preparing 2-hydroxy-3 : 5-diphenylpyrazine, this structure has been excluded for the compound, m. p. 197—198°, as the latter gives a 2 : 4-*dinitrophenylhydrazone* from which we conclude that it is 2-benzoyl-4(5)-phenylglyoxaline (I).

Experimental.

3-Hydroxy-2 : 5-diphenylpyrazine and 2-Benzoyl-4(5)-phenylglyoxaline.—(*a*) Phenylglyoxal hydrate (50 g.) in warm water (500 c.c.) was treated with ammonia (*d* 0·88; 50 c.c.), and the mixture was stirred for 30 minutes. The mixture was neutralised by the careful addition of dilute hydrochloric acid, and the orange-coloured solid was collected, washed with cold water, and extracted with hot 95% alcohol (200 c.c.). The residual solid (12 g.) was crystallised from glacial acetic acid and then from pyridine from which 3-hydroxy-2 : 5-diphenylpyrazine separated as pale yellow needles, m. p. 286°. It is soluble in 3N-sodium hydroxide (Found : C, 77·2; H, 5·1; N, 11·1. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·8; N, 11·3%). A suspension of 3-hydroxy-2 : 5-diphenylpyrazine (0·6 g.) in glacial acetic acid (4 c.c.) was treated with a solution of bromine (0·6 g.) in glacial acetic acid (7 c.c.), and the mixture was warmed until solution was complete. The solid which separated on cooling was recrystallised from alcohol, giving the bromo-derivative as yellow felted needles, m. p. 246° (Found : C, 58·5; H, 3·0; N, 8·6. Calc. for $C_{16}H_{11}ON_2Br$: C, 58·7; H, 3·4; N, 8·6%).

The alcoholic extract, obtained as described above, was evaporated, the solid (18 g.) dissolved in hot 3N-sodium hydroxide, and the filtered solution cooled. The crystalline solid which separated was recrystallised from aqueous pyridine, giving *2-benzoyl-4(5)-phenylglyoxaline* as soft iridescent yellow plates, m. p. 197—198° (Found : C, 77·8; H, 5·1; N, 11·3. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

The 2 : 4-*dinitrophenylhydrazone* separates from dilute acetic acid as small orange-red needles, m. p. 265° (Found : C, 61·5; H, 4·2; N, 19·4. $C_{22}H_{16}O_4N_6$ requires C, 61·7; H, 3·7; N, 19·6%).

A suspension of 2-benzoyl-4(5)-phenylglyoxaline (0·5 g.) in glacial acetic acid (3 c.c.) was shaken with a solution of bromine (1 c.c.) in acetic acid (5 c.c.) until solution was complete. The solution was diluted with water and the solid was collected, washed with water, and recrystallised from alcohol giving the *dibromo*-derivative as pale yellow needles, m. p. 248° (Found : C, 47·5; H, 2·6; N, 6·5. $C_{16}H_{10}ON_2Br_2$ requires C, 47·3; H, 2·5; N, 6·9%).

(*b*) A mixture of phenylglyoxal (4·02 g.) and ammonium formate (11·3 g.) was heated to 175° for 2 hours. The mixture was extracted with boiling water and then with boiling alcohol (10 c.c.). The residual solid was recrystallised from a large volume of alcohol from which 3-hydroxy-2 : 5-diphenylpyrazine separated as bright yellow plates (1·2 g.), m. p. 285—286° either alone or when mixed with the specimen described above. The monobromo-derivative separated from alcohol as yellow needles, m. p. 246° undepressed with the specimen prepared by method (*a*).

Evaporation of the alcohol mother liquor gave a solid (1·8 g.) which was crystallised, first from aqueous pyridine, and then from a little alcohol giving 2-benzoyl-4(5)-phenylglyoxaline as golden-yellow plates, m. p. 197—198° either alone or when mixed with the specimen prepared by method (*a*). The dibromo-derivative, m. p. and mixed m. p. 248°, separated from alcohol as yellow needles.

3-*Hydroxy*-2 : 5-*diphenylpyrazine and* 3 : 6-*Dichloro*-2 : 5-*diphenylpyrazine*.—DL-Phenylglycine anhydride (cf. Kossel, *Ber.*, 1891, **24**, 4145; Ovakimian, Kuna, and Levene, *J. Biol. Chem.*, 1940, **135**, 91) was prepared by heating DL-phenylglycine methyl ester (24 g.) at 140° for 16 hours. After cooling, the product was triturated with ether, and the solid (15 g.) recrystallised from ethylene glycol monoethyl ether from which the diketopiperazine separated as needles, m. p. 292—293° (sinters at 287°) (Found : C, 72·5; H, 5·7. Calc. for $C_{16}H_{14}O_2N_2$: C, 72·2; H, 5·3%). DL-Phenylglycine anhydride (10 g.) was heated under reflux with phosphoryl chloride (50 c.c.) for 2 hours. The excess of phosphoryl chloride was removed under reduced pressure, and the residue was triturated with ice water. The solid was collected and extracted with boiling alcohol (500 c.c.). The insoluble solid (filtrate *A*) was recrystallised from glacial acetic acid, giving 3-hydroxy-2 : 5-diphenylpyrazine as yellow prisms (0·53 g.), m. p. 283°, raised to 285° by recrystallisation from aqueous dioxan; its m. p. was not depressed when it was mixed with the specimen described above (Found : C, 77·0; H, 4·9; N, 11·7. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·8; N, 11·3%). The bromo-derivative separated from acetic acid as yellow felted needles, m. p. and mixed m. p. 245° (Found : C, 58·9; H, 3·5. Calc. for $C_{16}H_{11}ON_2Br$: C, 58·7; H, 3·4%).

The alcoholic filtrate *A* was concentrated to 200 c.c. and cooled. The solid separating (filtrate *B*) was recrystallised from alcohol from which 3 : 6-*dichloro*-2 : 5-*diphenylpyrazine* (2·96 g.) separated as needles, m. p. 159—160° (Found : C, 63·8; H, 3·5. $C_{16}H_{10}N_2Cl_2$ requires C, 63·8; H, 3·3%). This compound was readily soluble in acetone.

The filtrate *B* was evaporated, and the amorphous solid residue digested with methanol (50 c.c.), and the solid collected. This was recrystallised from glacial acetic acid, yielding a second crop of 3 : 6-dichloro-2 : 5-diphenylpyrazine (0·6 g.), m. p. 157—158° undepressed when mixed with the specimen described above. The methanolic mother liquor was evaporated to dryness and the resultant resin heated at 200° with powdered potassium hydroxide (10 g.) for 6 hours. The mixture was diluted with water and acidified with hydrochloric acid. The yellow solid was collected and boiled with glacial acetic acid, and the solution was filtered from silica. The filtrate deposited 3-hydroxy-2 : 5-diphenylpyrazine as yellow prisms (0·41 g.), m. p. and mixed m. p. 284°.

3-*Hydroxy*-2 : 5-*diphenylpyrazine*.—Sodium nitrite (0·1 g.) was added in small portions with stirring to concentrated sulphuric acid (1·5 c.c.) at 0°. The mixture was gradually heated to 60°. The clear solution was cooled to 0°, and treated with a solution of 3-amino-2 : 5-diphenylpyrazine (Newbold, Spring, and Sweeny, this vol., p. 300) (0·25 g.) in concentrated sulphuric acid (3 c.c.) added dropwise with stirring, the temperature being kept at or slightly below 0°. When the addition was complete, sodium nitrite (0·05 g.) was added, and the solution kept at 0° for 1 hour. The solution was poured on crushed ice (25 g.), and the mixture stirred until evolution of nitrogen ceased. The precipitated solid was collected and crystallised from glacial acetic acid giving 3-hydroxy-2 : 5-diphenylpyrazine (0·15 g.) as yellow-green prisms, m. p. 286° either alone or when mixed with the specimens described above.

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195. *Toxic Fluorine Compounds containing the* C–F *Link. Part III. Fluoroacetamide and Related Compounds.*

By F. J. BUCKLE, R. HEAP, and B. C. SAUNDERS.

An account is given of the preparation of fluoroacetamide and of a number of hitherto undescribed *N*-substituted derivatives. Fluoroacetamide, a stable crystalline compound, can be conveniently used as an analytical reference substance for the determination of fluorine in organic compounds.

Fluoromethyl cyanide is very readily converted into *fluoroacetimino ethyl ether hydrochloride* and the 2-*fluoroethyl* and the *phenyl* analogue.

The toxic action of these compounds is discussed.

FLUOROACETAMIDE was first mentioned by Swarts (*Bull. Soc. chim.*, 1896, **15**, 1134), but he gave no exact details for its preparation. In 1943 (Ministry of Supply Contract) we prepared this compound in high yield by the action of ammonia on methyl fluoroacetate. It is a highly

crystalline stable compound of sharp m. p., and it has proved useful for the identification of methyl fluoroacetate (MFA). Because of its stability and the fact that it can be obtained in a highly purified condition, it has proved to be of great value as an analytical standard for organic compounds containing fluorine. It has the advantage, too, that it contains nitrogen which can be determined independently. Being a solid, it was not possible to assess its toxicity by inhalation in comparison with MFA, but intravenous injection into rabbits showed that the two compounds were about equally toxic and produced the same type of convulsions.

By distilling the amide with phosphoric oxide at ordinary pressure, fluoromethyl cyanide was obtained as a colourless, mobile liquid. This compound had been obtained by Swarts (*Bull. Soc. chim. Belg.*, 1922, **31**, 364), who claimed that it was necessary to distil the amide with phosphoric oxide under reduced pressure and to collect the distillate at −50°. We have shown that neither of these elaborations is necessary. The toxicity of fluoromethyl cyanide on inhalation proved to be less than that of methyl fluoroacetate. The cyanide, however, did show the interesting property of being much more toxic to rabbits than to guinea-pigs, rats, and mice. The preparation of free fluoroacetic acid from methyl fluoroacetate *via* the barium salt was described in Part I (*J.*, 1948, 1773). An alternative and very convenient method for preparing the free acid consists in treating fluoroacetamide with nitrous fumes, the pure acid being produced in 90% yield. The two methods may be summarised thus :

$$F\cdot CH_2\cdot CO_2Me \xrightarrow{90\cdot7\%} (F\cdot CH_2\cdot CO_2)Ba \text{ (crude)} \xrightarrow{82\cdot7\%} F\cdot CH_2\cdot CO_2H \text{ (pure)} \quad \textit{Overall yield } 75\cdot0\%$$

$$F\cdot CH_2\cdot CO_2Me \xrightarrow{100\%} F\cdot CH_2\cdot CO\cdot NH_2 \text{ (crude)} \xrightarrow{90\cdot0\%} F\cdot CH_2\cdot CO_2H \text{ (pure)} \quad \textit{Overall yield } 90\cdot0\%$$

It is noteworthy that the L.D. 50 by intravenous injection for fluoroacetic acid, methyl fluoroacetate, and the amide are almost identical (0·25 mg./kg. for rabbits).

N-*Methylfluoroacetamide* and its *N*-nitroso-derivative were prepared by standard methods and found to have toxicities which indicated the ready hydrolysis of these compounds by the animal body to fluoroacetic acid.

The group $Cl\cdot CH_2\cdot CH_2\cdot N<$ occurs in the powerful vesicant $CH_3\cdot N(CH_2\cdot CH_2Cl)_2$. It was decided therefore to introduce this group into the fluoroacetamide molecule in the hope of combining vesicant properties with the delayed convulsant action of the fluoroacetates. For this purpose N-2-*hydroxyethylfluoroacetamide* (I) was prepared by the action of monoethanolamine on methyl fluoroacetate and was readily converted into N-2-*chloroethylfluoroacetamide* (II) by the action of thionyl chloride.

$$CH_2F\cdot CO_2Me + NH_2\cdot CH_2\cdot CH_2\cdot OH \longrightarrow \underset{\text{(I.)}}{CH_2F\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot OH} \longrightarrow \underset{\text{(II.)}}{CH_2F\cdot CO\cdot NH\cdot CH_2\cdot CH_2Cl}$$

N-2-Chloroethylfluoroacetamide was also prepared by the direct action of 2 mols. of fluoroacetyl chloride on ethanolamine, although we carried out this reaction with the intention of preparing 2-(fluoroacetamido)ethyl fluoroacetate, $CH_2F\cdot CO_2CH_2\cdot CH_2\cdot NH\cdot CO\cdot CH_2F$. Injection of (II) into mice showed that the L.D. 50 was similar to that of fluoroacetamide or of fluoroacetic acid, and the symptoms produced appeared to be identical in each case; (II), however, showed no vesicant action. It is probable then that hydrolysis of the molecule occurs *in vivo*, resulting in the formation of fluoroacetic acid and the relatively harmless 2-chloroethylamine.

By reactions similar to the above we also prepared NN-*di*-(2-*hydroxyethyl*)*fluoroacetamide* and NN-*di*-(2-*chloroethyl*)*fluoroacetamide*.

It was hoped that the action of bromine and potassium hydroxide solution on fluoroacetamide might give rise to the hitherto undescribed fluoromethylamine. Under the conditions employed, no fluoromethylamine was obtained, but a crystalline solid containing both fluorine and nitrogen was produced. Analysis and general reactions showed that it was N-*fluoroacetyl*-N′-*fluoromethylurea*. This reaction then is exactly analogous to Hofmann's preparation of the corresponding chloro-compound from chloroacetamide (*Ber.*, 1885, **18**, 2735). Toxicity by injection into mice showed an L.D. 50 of about 60 mg./kg.

We then directed our attention to the properties of fluoromethyl cyanide, as it seemed likely, on theoretical grounds, that it would undergo certain addition reactions very readily. Alcohol and dry hydrogen chloride readily converted it into *fluoroacetimino ethyl ether hydrochloride* (III), which was converted into the *amidine* (IV) by means of alcoholic ammonia. Similar condensation of the cyanide with 2-fluoroethanol and phenol yielded *fluoroacetimino-2-fluoroethyl ether hydrochloride* (V; R = $CH_2\cdot CH_2F$) and the corresponding *imino phenyl ether hydrochloride*

(V; R = Ph) respectively. Analogous experiments were carried out with methyl cyanide, and it was established that the rate of formation of the imino ether hydrochlorides was much slower

$F{\cdot}CH_2{\cdot}C(OEt){:}\overset{+}{N}H_2\bar{C}l$ (III.) $F{\cdot}CH_2{\cdot}C(NH_2){:}\overset{+}{N}H_2\bar{C}l$ (IV.) $F{\cdot}CH_2{\cdot}C(OR){:}\overset{+}{N}H_2\bar{C}l$ (V.) $\overset{-\delta}{F}\leftarrow CH_2\leftarrow\overset{+\delta}{C}\equiv\overset{-\delta}{N}$ (VI.)

with this than with the fluoro-substituted analogue; *e.g.*, on a 0·1M. scale separation of (III) occurred within 10 minutes, and the mixture became very hot although cooled in ice, but with methyl cyanide, although absorption of hydrogen chloride was just as fast, the solution became only very slightly warm and no solid separated for several hours. This difference in reactivity was even more noticeable in the condensations with phenol.

This enhanced reactivity of fluoromethyl cyanide is undoubtedly due to the inductive effect of the fluorine atom which produces an electron deficit on the carbon atom linked to the nitrogen, and presumably increases still further the polarity of the carbon–nitrogen bond, so that the electron displacements can be pictured as (VI). The increased polarity of the CN bond will obviously facilitate polar addition of hydrogen chloride and alcohols (or phenols).

Compounds (III), (IV), and (V; R = $CH_2{\cdot}CH_2F$ and R = Ph) were tested pharmacologically by subcutaneous injection into mice. Results obtained are shown in the accompanying table.

Compound.	Toxicity towards mice.
(III)	Comparable with that of methyl fluoroacetate
(V; R = Ph)	,, ,, ,,
(IV)	,, ,, ,,
(V; R = $CH_2{\cdot}CH_2F$)	Comparable with that of 2-fluoroethyl fluoroacetate

It was to be expected that the imino ether hydrochlorides would be hydrolysed in the body to give the corresponding fluoroacetate and ammonium chloride, and the toxicities should be roughly the same as those of the fluoroacetates. The results show this to be the case. The compound (V; R = $CH_2{\cdot}CH_2F$) was expectedly more toxic than the other compounds, as this would form 2-fluoroethyl fluoroacetate on hydrolysis, which is known to be twice as toxic as methyl or ethyl fluoroacetate (McCombie and Saunders, *Nature*, 1946, **158**, 382).

Experimental.

Fluoroacetamide.—Pure methyl fluoroacetate (20 g.) was cooled in ice-water and excess of aqueous ammonia (20 c.c., *d* 0·88) was added. The crystalline precipitate (15 g.) which separated was filtered off after an hour and dried. It was practically pure. It could be recrystallised from chloroform, or from chloroform–light petroleum (b. p. 100°), forming long needles, m. p. 108°. Further crops of crystals were obtained from the original ammoniacal filtrate by evaporation under reduced pressure (1 g.) and finally by evaporation to dryness (2·7 g.). The last specimen (dried in a vacuum over sulphuric acid) was not so pure as the others; total yield 16·7 g. (100%). The amide was obtained in very pure condition by sublimation; m. p. 108° (Found: C, 31·0; H, 4·9; N, 18·2; F, 24·7. Calc. for C_2H_4ONF: C, 31·2; H, 5·2; N, 18·2; F, 24·7%). This can serve as an analytical standard (*Analyst*, 1948, **73**, 434).

Fluoromethyl Cyanide.—A mixture of fluoroacetamide (10 g., dried in a vacuum over concentrated sulphuric acid) and phosphoric oxide (17·5 g.) was placed in a flask fitted with a water-condenser, and heated in an oil-bath to 110° at which temperature the reaction started. The bath was then kept at 160° until the cyanide ceased to distil; yield 5 g. (65·2%). This product was distilled through a column and practically the whole of it came over at 80°/760 mm. (Found: N, 23·3. Calc. for C_2H_2NF: N, 23·7%).

Fluoroacetic Acid (*New Method*).—Nitrous fumes, prepared from nitric acid and arsenous oxide, and dried over calcium chloride and phosphoric oxide, were passed into crystalline fluoroacetamide (10 g.) cooled in ice. Heat was evolved and the mixture liquefied as the reaction proceeded. The passage of nitrous fumes was continued for about an hour after the mixture had completely liquefied. The black liquid thus obtained was heated to boiling while a stream of dry nitrogen was passed through in order to remove excess of nitrous fumes. Excess of phosphoric oxide (6 g.) was added with cooling, and the mixture set aside overnight. Dry nitrogen was again passed through at the b. p. until the nitrous fumes were completely removed. In this way, water and nitric acid were completely eliminated. The product was then distilled at ordinary pressure, and the fraction of b. p. 164·5—165° collected. This solidified to a mass of fine needles; m. p. 31°; yield 9 g. (90%) (Found: F, 24·3. Calc. for $C_2H_3O_2F$: F, 24·3%).

N-*Methylfluoroacetamide.*—Methyl fluoroacetate (10 g.) was cooled in ice-water, and excess of methylamine added (10 g. of 33% aqueous solution). No solid separated overnight, and the solution was therefore submitted to vacuum distillation and the solid residue dried in a vacuum over concentrated sulphuric acid. The impure product (100% yield) recrystallised from chloroform–light petroleum (b. p. 100°) in long deliquescent needles, and was dried over sulphuric acid, calcium chloride and paraffin wax; m. p. 64°; yield of recrystallised *amide*, 7·5 g. (75%) (Found: C, 39·9; H, 6·7; N, 15·2. C_3H_6ONF requires C, 39·6; H, 6·1; N, 15·4%).

N-*Nitroso*-N-*methylfluoroacetamide.*—Nitrous fumes were passed into *N*-methylfluoroacetamide (12 g.), and the excess then driven off by heating the product in a stream of nitrogen. The residue was fractionated under reduced pressure; b. p. 84°/14 mm.; yield 7 g. The compound contained nitrogen and fluorine and gave the Liebermann nitroso-reaction.

NN-*Di*-(2-*chloroethyl*)*fluoroacetamide.*—Methyl fluoroacetate (20 g.) and diethanolamine (23 g.) were

mixed, and after a time the mixture became homogeneous with only slight evolution of heat. As the crude *NN*-di-(2-hydroxyethyl)fluoroacetamide thus obtained decomposed on distillation (142°/0·2 mm.), it was used without further treatment for the next stage. The crude hydroxy-amide was dissolved in chloroform (100 c.c.), and thionyl chloride dissolved in chloroform (100 c.c.) was added down a reflux condenser. [The amount of thionyl chloride used was 88 g., *i.e.*, rather more than sufficient (10% excess) to react with both hydroxyl groups of the amide and with the methyl alcohol formed in the first part of the reaction.] After the addition was complete, the mixture was heated under reflux for 4 hours. Most of the chloroform was distilled off at room pressure. At 0·1 mm. a fraction was obtained of b. p. 111°. This was redistilled, and NN-*di*-(2-*chloroethyl*)*fluoroacetamide* was obtained as a colourless viscous liquid of b. p. 102°/0·04 mm.; yield 17·5 g. (40%) (Found: Cl, 35·3; N, 7·1. $C_6H_{10}ONCl_2F$ requires Cl, 35·15; N, 6·9%).

N-2-*Hydroxyethylfluoroacetamide*.—Methyl fluoroacetate (10 g.) and ethanolamine (6·5 g.) were carefully mixed. Considerable heat was evolved, and the mixture was then allowed to cool spontaneously. The methyl alcohol (theoretical yield) was distilled off at room pressure, and the residue then fractionated under reduced pressure. The *amide* was obtained as a viscous, colourless distillate; b. p. 114°/0·1 mm.; yield 12 g. (91·4%). It solidified to a white solid, m. p. *ca.* 21° (Found: N, 11·5. $C_4H_8O_2NF$ requires N, 11·6%).

N-2-*Chloroethylfluoroacetamide*.—(i) Thionyl chloride (9·5 g.), dissolved in dry chloroform (10 c.c.), was slowly run down a reflux condenser into the hydroxy-amide (9·5 g.), also dissolved in dry chloroform (10 c.c.). The mixture was left for some hours, and the chloroform distilled off in the cold at 15 mm. The solid residue thus obtained was distilled and had b. p. 77°/0·3 mm. The N-2-*chloroethylfluoroacetamide* solidified and was recrystallised from chloroform; m. p. 65°. It sublimed slowly on heating. Yield 9·5 g. (87·1%) (Found: N, 9·7; Cl, 25·0. C_4H_7ONClF requires N, 10·0; Cl, 25·4%).

(ii) [This experiment was originally designed to afford 2-(fluoroacetamido)ethyl fluoroacetate.] Fluoroacetyl chloride (16 g., 0·16 mol.) was slowly added to monoethanolamine (5 g., 0·08 mol.) in a flask fitted with a condenser and calcium chloride tube. There was an initial vigorous reaction which subsided when about half of the acid chloride had been added. The flask was then heated in an oil-bath to 70°, which caused a further copious evolution of hydrogen chloride. Finally, the temperature of the oil-bath was raised to 100° to complete the reaction. The product was then distilled (b. p. 125—130°/17 mm.), forming a colourless liquid which crystallised to a white solid (8·9 g.; 70% based on monoethanolamine used). The crystals thus obtained were recrystallised from benzene and dried in an Abderhalden apparatus at 1 mm./40—60°; m. p. 64·5° [Found: C, 34·6; H, 5·4; N, 10·2; F, 13·66; *M* (Rast), 144. C_4H_7ONClF requires C, 34·3; H, 5·0; N, 10·0; F, 13·6%; *M*, 139·5].

Action of Bromine and Potassium Hydroxide on Fluoroacetamide.—(i) Fluoroacetamide (11 g.) and bromine (25 g., 7·5 c.c.) were mixed in a flask immersed in cold water. Potassium hydroxide (10% aqueous solution) was added with shaking until the mixture became pale yellow. The product was then run into potassium hydroxide (30 g.), dissolved in water (55 c.c.). The mixture (the temperature of which was not allowed to rise above 70°) was slowly distilled into dilute hydrochloric acid. The distillate on evaporation gave mainly ammonium chloride, but traces of fluorine were detected, probably due to ammonium fluoride.

(ii) The above experiment was repeated but with only 20 g. of potassium hydroxide. The gas evolved during the distillation was collected in liquid air. A white solid was obtained which, on removal from the liquid air, slowly evaporated without liquefying. It proved to be mainly carbon dioxide contaminated with traces of hydrogen fluoride. The non-volatile residue was extracted with ether, dried (Na_2SO_4), filtered, and the ether distilled off. *N-Fluoromethyl-N′-fluoroacetylurea* was obtained as a solid which recrystallised from benzene in small, colourless, well-defined needles; m. p. 84° (Found: C, 31·85; H, 4·3; F, 25·6. $C_4H_6O_2N_2F_2$ requires C, 31·6; H, 3·9; F, 25·0%). When heated with sodium hydroxide, it evolved ammonia.

Fluoroacetimino Ethyl Ether Hydrochloride.—Dry fluoromethyl cyanide (6 g., 0·1 mol.) was mixed with absolute alcohol (4·6 g., 0·1 mol.) in a flask protected by a calcium chloride tube, and cooled in ice–salt. Dry hydrogen chloride was passed into the mixture, which in spite of external cooling, became very hot, and a solid began to separate. The mixture became a solid mass within 5 minutes, the gain in weight then being 3·5 g. (0·097 mol. of hydrogen chloride). The solid mass was ground, washed with dry ether, and the *hydrochloride* dried in a vacuum (Found: Cl′, 24·85. C_4H_9ONClF requires Cl′, 25·1%).

Fluoroacetamidine Hydrochloride.—The foregoing hydrochloride (6 g., 0·05 mol.) was ground in a dry mortar with absolute alcohol (2 c.c.) and stirred mechanically with 9% absolute alcoholic ammonia (25 c.c.; 0·13 mol. of NH_3) for 3 hours. A faint pink colour developed, the ammonium chloride formed was filtered off, and the filtrate evaporated on a steam-bath. A dark brown colour developed, and on cooling a mass of crystals separated. The *hydrochloride* was recrystallised twice from absolute alcohol, yielding colourless needles, m. p. 161—162° (decomp.) (Found: F, 16·32. $C_2H_6N_2ClF$ requires F, 16·9%). The *picrate* was prepared by mixing cold saturated alcoholic solutions of picric acid and the amidine hydrochloride; it separated as yellow needles in a few minutes, and was recrystallised twice from alcohol; m. p. 222—224° (decomp.) (Found: C, 31·45; H, 2·3; N, 22·6. $C_8H_6O_7N_5F$ requires C, 31·5; H, 2·6; N, 22·95%).

Fluoroacetimino 2-Fluoroethyl Ether Hydrochloride.—Dry fluoromethyl cyanide (6 g., 0·1 mol.) and redistilled fluoroethyl alcohol (6·4 g., 0·1 mol.) were mixed in a flask cooled in ice and salt and fitted with an inlet tube, the exit tube being protected from moisture by a calcium chloride tube. Dry hydrogen chloride was passed in with occasional shaking for 7 minutes, the mixture then becoming very hot and solidifying to a mass of white crystals. The gain in weight was 3·0 g. (0·08 mol. of hydrogen chloride). The mixture could not be broken up sufficiently to allow thorough mixing of the product, and the excess of fluoroethyl alcohol and fluoromethyl cyanide was removed by grinding the product to a fine powder with dry ether; the *hydrochloride* was filtered off and dried (Found: Cl, 21·4. $C_4H_8ONClF_2$ requires Cl, 21·9%).

Fluoroacetimino Phenyl Ether Hydrochloride.—Phenol (9·4 g., 0·1 mol.) was dissolved in dry fluoromethyl cyanide (5·9 g., 0·1 mol.), and dry hydrogen chloride passed into the mixture for 15 minutes,

under the same conditions as above. The gain in weight was 3·6 g. (0·1 mol. of hydrogen chloride). The mixture became very viscous and after a few minutes deposited white rosettes of crystals, the whole mass becoming solid in a few hours. The crystalline *ether hydrochloride* was broken up, ground with dry ether, filtered off, and dried (Found: Cl, 19·2. C_3H_9ONClF requires Cl, 18·9%).

An analogous experiment was performed with dry methyl cyanide (4·1 g., 0·1 mol.) and phenol (9·4 g., 0·1 mol.), but after ½ hour the amount of hydrogen chloride absorbed was only 0·1 g. (0·28 mol.), and only a very few crystals were deposited after 14 hours.

We wish to thank the Chief Scientist of the Ministry of Supply for permission to publish this paper. A description of the properties of fluoroacetamide, its *N*-derivatives, and of fluoromethyl cyanide appeared in Reports on Fluoroacetates to the Ministry of Supply by McCombie and Saunders, No. 2 (Feb. 17, 1943) and No. 5 (May 30, 1943), and a preliminary account appeared in *Nature*, 1946 (*loc. cit.*).

We are grateful to Dr. W. J. O'Connor, of the Department of Pharmacology, Cambridge, and to Dr. B. A. Kilby for toxicity tests on small animals.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 20th*, 1948.]

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196. *Toxic Fluorine Compounds Containing the* C–F *Link. Part IV.* (a) 2-*Fluoroethyl Fluoroacetate and Allied Compounds.* (b) 2 : 2′-*Difluorodiethyl Ethylene Dithioglycol Ether.*

By B. C. SAUNDERS and G. J. STACEY.

2-*Fluoroethyl fluoroacetate* (I) is a stable liquid of high toxicity. It is about twice as potent (weight for weight) as either fluoroethanol or methyl fluoroacetate. The synthesis and examination of six related esters is described, none of which is as toxic as (I).

The synthesis of 2 : 2′-difluorodiethyl ethylene dithioglycol ether ("sesqui-fluoro H") is described. It is a liquid which is neither vesicant nor produces "fluoroacetate-like" symptoms in the animal body.

IN view of the fact that fluoroethanol is as toxic as methyl fluoroacetate (or as fluoroacetic acid), it seemed worth while preparing a compound in which the "active" parts of these molecules were combined, in the hope of obtaining a compound of increased potency. Such a compound is 2-*fluoroethyl fluoroacetate* (I), first prepared and described by us in 1943 (Report No. 4 on Fluoroacetates by McCombie and Saunders, to the Ministry of Supply, April 15, 1943). This ester was readily prepared by the action of fluoroacetyl chloride (Part I, *J.*, 1948, 1773) on fluoroethanol (Part II, this vol., p. 773). It is a stable, mobile liquid possessing an extremely faint odour.

In accordance with expectation, 2-fluoroethyl fluoroacetate was found to possess greatly enhanced toxic properties. The L.C. 50 by inhalation for rabbits was 0·05 mg./l. This shows that it is about twice as toxic (weight for weight) as fluoroethanol or methyl fluoroacetate. This seems to indicate that the toxicity of 2-fluoroethyl fluoroacetate cannot be due entirely to that of its hydrolysis products according to the equation $CH_2F{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F + H_2O = CH_2F{\cdot}CO_2H + CH_2F{\cdot}CH_2{\cdot}OH$, for if this were the case the L.C. 50 would be approximately equal to that of either fluoroethanol or methyl fluoroacetate. 2-Fluoroethyl fluoroacetate must therefore possess toxic properties *per se* and this may be connected with the two "active" ends of the molecule. Subcutaneous injection into mice also showed the compound to be about twice as toxic as methyl fluoroacetate. With other animals this difference was not always so apparent.

In order to determine whether this increase in toxicity was necessarily bound up with the presence of two fluorine atoms in the molecule, a series of structurally related esters was prepared and examined. The first obvious simplification was to investigate 2-fluoroethyl acetate (II). [Ethyl fluoroacetate has been shown to have toxic properties almost identical with those of the methyl ester ("MFA"), Part I, *loc. cit.*] By inhalation, (II) produced all the usual "fluoroacetate-like" symptoms, and appeared to be just slightly less toxic than methyl fluoroacetate.

2-*Chloroethyl fluoroacetate* (III), at a concentration of 0·31 mg./l., killed 92% of a batch of rabbits, guinea-pigs, and rats, and at 0·10 mg./l., 54%. These (and other figures obtained) indicate that the compound was more toxic than MFA, but not as toxic as (I).

It is of interest that (III) and 2-*fluoroethyl chloroacetate* (IV) have identical boiling points. The toxicities of these two isomers were also found to be almost identical.

The synthesis of 2-fluoroethyl fluoroacetate mentioned above entails a double fluorination, depending ultimately upon the conversion of chlorohydrin into fluoroethanol and of methyl

chloroacetate into methyl fluoroacetate. Attempts were therefore made to prepare (I) by direct fluorination of 2-chloroethyl chloroacetate. By the action of potassium fluoride in a rotating autoclave under pressure on the chloro-ester, only low yields of (I) were obtained. Although the conditions of fluorination were varied considerably, yields higher than about 14% were not obtained. Even then the product was slightly contaminated with the partly fluorinated esters. It seems, therefore, that the double fluorination method is much more satisfactory.

Phenyl fluorothiolacetate (V) had an L.D. 50 of about 80 mg./kg. for subcutaneous injection into mice, hence its toxicity was about one-tenth of that of MFA.

2-*Chloroethyl fluorothiolacetate* (VI) was prepared in the hope that it might combine vesicant properties (cf. " mustard gas ") with the convulsant properties of the fluoroacetates. It was an unpleasant-smelling oil which, however, was devoid of vesicant action. The L.D. 50 for subcutaneous injection into mice was 17·5 mg./kg. It was therefore less toxic than MFA. By inhalation the toxicity was even lower, though this may have been due to its relative nonvolatility (b. p. 100°/29 mm.).

In view of the irritant action exerted by some vinyl and allyl compounds, *allyl fluoroacetate* (VII) was prepared and examined. It proved to be nearly as toxic by inhalation as MFA, and in addition it had an irritant effect on the animals submitted to it. Slow breathing and gasping were shown towards the end of the exposure. Typical " fluoroacetate-type " convulsions were also observed. Subcutaneous injection of a normal saline solution into mice showed that the L.D. 50 was 6 mg./kg., this figure being very close to that for MFA.

The above may be conveniently summarised in the following table :

Ester.	Formula.	Toxicity compared with methyl fluoroacetate.
Ethyl fluoroacetate	$CH_2F{\cdot}CO_2Et$	Similar
2-Chloroethyl fluoroacetate	$CH_2F{\cdot}CO_2CH_2{\cdot}CH_2Cl$ (III.)	Rather higher
2-Fluoroethyl acetate	$CH_3{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F$ (II.)	Less
2-Fluoroethyl chloroacetate	$CH_2Cl{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F$ (IV.)	Rather higher
2-Fluoroethyl fluoroacetate	$CH_2F{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F$ (I.)	Twice
Phenyl fluorothiolacetate	$CH_2F{\cdot}CO{\cdot}SPh$ (V.)	Low
2-Chloroethyl fluorothiolacetate ...	$CH_2F{\cdot}CO{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl$ (VI.)	Lower by injection; considerably lower by inhalation
Allyl fluoroacetate	$CH_2F{\cdot}CO_2C_3H_5$ (VII.)	Very slightly less

In view of the powerful vesicant action of 2 : 2′-dichlorodiethyl ethylene dithioglycol ether (" sesqui-H "), we decided in 1943 (Report No. 8 on Fluoroacetates by McCombie and Saunders) to prepare the corresponding fluorine analogue. Earlier workers had failed to achieve the synthesis of this compound. Our preparation consisted in treating bromofluoroethane with sodium hydrogen sulphide. The resulting fluoroethanethiol (VIII) was not isolated, but was converted directly into the sodium mercaptide (IX). This was heated under reflux with an alcoholic solution of bromofluoroethane, and 2 : 2′-*difluorodiethyl ethylene dithioglycol ether* (1 : 8-difluoro-3 : 6-dithiaoctane) (X) thus obtained.

$$\text{(VIII.)}\quad CH_2F{\cdot}CH_2{\cdot}SH \longrightarrow CH_2F{\cdot}CH_2{\cdot}SNa \quad \text{(IX.)}$$

$$2CH_2F{\cdot}CH_2{\cdot}SNa + CH_2F{\cdot}CH_2Br \longrightarrow CH_2F{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2F \quad \text{(X.)}$$

This reaction is very interesting in view of the unreactivity of the halogen atoms in bromofluoroethane toward many reagents (Part II, *loc. cit.*). It may well be, however, that the reaction is not as simple as that represented above.

In order to prove the identity of (X), it was synthesised in a different manner. Ethylene dibromide was converted into ethylene dithiol, which was then heated with bromofluoroethane in the presence of sodium hydroxide. The yield by this method was small and quantities of dithian were also produced.

Experimental.

2-*Fluoroethyl Fluoroacetate*.—Fluoroacetyl chloride (9·7 g., 0·1 mol.), prepared by the method given in Part II (*loc. cit.*), was added slowly to fluoroethyl alcohol (8·0 g., 0·125 mol.); heat was evolved and external cooling was applied. When the addition was complete, the mixture was heated under reflux for 30 minutes, in an oil-bath at 110—120°. The product was then cooled in ice-water and poured into about 15 c.c. of ice-cold 20% aqueous sodium carbonate. The oil which separated was removed, the aqueous layer extracted with ether, the extracts added to the oil, and the whole washed with water and dried (Na_2SO_4). After distillation of the ether, the residue was fractionated and nearly all of it came over at 92—95°/67 mm.; yield 9·6 g. (77·4%). On redistillation the 2-*fluoroethyl fluoroacetate* had b. p. 90·5—91°/58 mm. (Found : F, 31·1. $C_4H_6O_2F_2$ requires F, 30·6%). It is an almost odourless, mobile liquid, $d_4^{10°}$ 1·3047, $d_4^{15°}$ 1·2975, $d_4^{20°}$ 1·2906, $d_4^{25°}$ 1·2836; f. p. −25·4°; vap. press. : 0°, 0·45 mm.; 15°, 1·28 mm.; 30°, 3·29 mm.

2-Chloroethyl Fluoroacetate.—Fluoroacetyl chloride (19·3 g., 0·2 mol.) was added slowly to ethylene chlorohydrin (18·1 g., 0·225 mol.) without external cooling. The product was then warmed under reflux in an oil-bath at 100° for 30 minutes, cooled, and carefully added to ice-cold sodium carbonate (25 c.c., 20%). The oil which formed was separated, the aqueous layer extracted with ether, and the ethereal extracts added to the oil, the whole being washed once before being dried (Na_2SO_4). After distillation of the ether, the residual liquid distilled at 104—106°/56 mm. This was redistilled, and the fraction of b. p. 78·5°/15 mm. was collected; yield 21·6 g. (76·9%). *2-Chloroethyl fluoroacetate* is a colourless mobile liquid, almost insoluble in water, and possessing a very faint odour; b. p. 178—179°/760 mm.; f. p. −8·7° ± 0·5° (Found: C, 34·2; H, 3·86; Cl, 25·1. $C_4H_6O_2ClF$ requires C, 34·2; H, 4·12; Cl, 25·23%); $d_4^{10°}$ 1·3361, $d_4^{15°}$ 1·3295, $d_4^{20°}$ 1·3230, $d_4^{25°}$ 1·3160; vap. press. at 15°, 0·85 mm.

2-Fluoroethyl Chloroacetate.—To fluoroethyl alcohol (16·0 g., 0·25 mol.), placed in a flask under reflux, chloroacetyl chloride (33·8 g., 0·2 mol.) was added slowly, very little external cooling being necessary. When the addition was complete, the mixture was heated under reflux on the water-bath for 30 minutes, cooled, and added to aqueous sodium carbonate (25 c.c., 20%). The heavy oil which separated was run off, and the aqueous layer extracted with carbon tetrachloride, the extracts added to the oil, and the whole washed once with water, and dried ($CaCl_2$). The carbon tetrachloride was distilled off, and the *2-fluoroethyl chloroacetate* distilled under reduced pressure; almost all of it came over at 78—79°/15 mm.; yield 26·1 g. (92·8%); b. p. 178°/760 mm. (b. p. of 2-chloroethyl fluoroacetate is 178—179°/760 mm.) (Found: F, 14·1. $C_4H_6O_2ClF$ requires F, 13·52%).

2-Fluoroethyl chloroacetate was also prepared as follows: Chloroacetic acid (20 g., 0·2 mol.), fluoroethyl alcohol (25 g., 0·4 mol.), and sulphuric acid (2·5 c.c.) were heated under reflux for 6 hours at 120°. The product was cooled, diluted with water, the oily layer separated, and the aqueous layer extracted with ether. The oil and the ether extracts were combined, dried (Na_2SO_4), filtered, and the ether distilled off; almost the entire residue had b. p. 179—181°; yield 23 g.

Fluorination of 2-Chloroethyl Chloroacetate.—A mixture of 2-chloroethyl chloroacetate (105 g., 0·67 mol.) and dry, powdered potassium fluoride (116 g., 2 mols.) was heated in a rotating autoclave. The period of heating and the temperature were varied. On cooling, the viscous brown material was extracted with acetone or acetone–ether, the low-boiling solvent distilled off, and the residual liquid fractionated. As no very definite fractions were obtained, the distillate was collected between certain limits, designed to separate as far as possible the difluorinated from the monofluorinated compounds formed. The first distillation was carried out under reduced pressure, up to the temperature of the b. p. of the unchanged ester. This distillate was then fractionated under ordinary pressure. The accompanying table gives some of the results obtained.

Reference data. 2-Chloroethyl chloroacetate, b. p. 202°. 2-Chloroethyl fluoroacetate, b. p. 178—179°. 2-Fluoroethyl chloroacetate, b. p. 178°. 2-Fluoroethyl fluoroacetate, b. p. 158°.

Temp. of reaction.	Time of heating, hrs.	Final fractionation. Temp.[a]	Yield, g.	Temp.[b]	Yield, g.	Temp.[c]	Yield, g.
200—210°	6	Up to 152°	3·6	152—170°	10·7	170—173°	1·9
225	2½	Up to 150	4·5	150—168 (mainly 158—165)	10·9	168—185 (mainly 174—176)	15·4
180—185	10	Up to 150	1·9	150—168	2·2	168—190 (mainly 174—178)	25·5
250—260	3	← ill defined →					
225—230	7	← ill defined →					

The middle fraction (*b*) in each of the above distillations was essentially 2-fluoroethyl fluoroacetate. The compound, however, could not be obtained pure, being always slightly contaminated with the chloro-esters. The best yield was 10·9 g. (13·4%).

2-Fluoroethyl Acetate.—Acetyl chloride (24·5 g.) was added slowly to fluoroethyl alcohol (20 g.). Much heat was evolved, and when the reaction subsided, the mixture was heated under reflux for 30 minutes and then distilled. 2-Fluoroethyl acetate was obtained in almost theoretical yield; b. p. 118—119°/760 mm. (Found: F, 18·21. Calc. for $C_4H_7O_2F$: F, 17·92%).

Phenyl Fluorothiolacetate (S-*Fluoroacetylthiophenol*).—A mixture of thiophenol (5 g.) and fluoroacetyl chloride (5 g.; *i.e.*, a slight excess) was heated in an oil-bath, the temperature being raised slowly (1 hour) to 220° and then kept there for 20 minutes. The mixture darkened as the temperature rose. The product was then distilled under reduced pressure, and the fraction of b. p. 120—140°/18 mm. was collected. On standing overnight, this solidified to colourless needle-shaped crystals. The *fluorothiolacetate* was recrystallised from a small volume of alcohol and ice-cooled before being collected; m. p. 36·5—37·5°; b. p. 132°/18 mm.; yield of recrystallised material, 1·7 g. (21%) (Found: S, 18·97; F, 10·95. C_8H_7OSF requires S, 18·82; F, 11·17%). The compound was insoluble in cold water and very soluble in alcohol and in acetone.

2-Chloroethyl Fluorothiolacetate.—Fluoroacetyl chloride (10 g., 0·1 mol.) was added to chloroethylthiol (10 g., 0·1 mol.). No reaction occurred in the cold: the mixture was therefore heated at 150° for 30 minutes under reflux. The temperature was then slowly raised to 190° and the heating stopped when no more hydrogen chloride was evolved. On distillation a colourless liquid, b. p. 104—105°/33 mm., was obtained; yield 13·5 g. (63%). The *2-chloroethyl fluorothiolacetate* thus obtained had an unpleasant odour. It was insoluble in water, soluble in ethyl alcohol, ether, or acetone (Found: Cl, 22·28; F, 11·75; S, 20·40. C_4H_6OSClF requires Cl, 22·67; F, 12·14; S, 20·45%).

Allyl Fluoroacetate.—Fluoroacetyl chloride (20 g., 0·2 mol.) was added slowly from a dropping-funnel to allyl alcohol (11·6 g., 0·2 mol.) in a flask, cooled in ice, and fitted with a reflux condenser. Hydrogen

chloride was evolved in the cold and there was a slight rise in temperature. When the evolution of hydrogen chloride ceased, the mixture was heated at 130° (oil-bath) until no more gas came off. The resulting liquid was distilled, and the fraction, b. p. 136—137°/760 mm., was collected and found to be chlorine-free; yield 10·5 g. (46%). *Allyl fluoroacetate* immediately decolourised bromine water in the cold. It was insoluble in water, but readily soluble in alcohol, ether, or acetone (Found: F, 16·45. $C_5H_7O_2F$ requires F, 16·1%).

2 : 2′-*Difluorodiethyl Ethylene Dithioglycol ether.*—(1) Sodium (6·9 g., 0·3 mol.) was dissolved in ethyl alcohol (120 c.c.), and the resultant solution saturated with a stream of hydrogen sulphide (washed with water and dried by passage through calcium chloride). The solution of sodium hydrogen sulphide so obtained was added, in small portions, with shaking, to 1-bromo-2-fluoroethane (38·1 g., 0·3 mol.) dissolved in alcohol (30 c.c.). The whole was then heated under reflux on the water-bath for 15 minutes, cooled, and filtered. To the filtrate was added, slowly, a solution of sodium (4·6 g., 0·2 mol.) in ethyl alcohol (80 c.c.), and the whole added to a solution of 1-bromo-2-fluoroethane (25·4 g., 0·2 mol) in ethyl alcohol (30 c.c.). The mixture was heated under reflux for 15 minutes, cooled, and filtered. The alcohol was distilled from the filtrate under reduced pressure: during the process, a quantity of solid separated. The residual liquid was distilled and came over at 142—146°/22 mm. (Usually a small quantity of dithian sublimed over as well and there was also a higher-boiling liquid left.) The distillate was redistilled, and the fraction, b. p. 138—139°/17 m., was collected; yield 10·4 g. After three distillations the 2 : 2′-*difluorodiethyl ethylene dithioglycol ether* was obtained free from dithian and then had b. p. 139°/17 mm. (Found: S, 35·0; F, 20·9. $C_6H_{12}S_2F_2$ requires S, 34·4; F, 20·4%).

(2) Sodium (14·4 g., 0·625 mol.) was dissolved in alcohol (250 c.c.), and the solution saturated with hydrogen sulphide and added, in small quantities at a time, to ethylene dibromide (49·0 g., 0·25 mol.) in alcohol (30 c.c.). The mixture was heated under reflux for 1½ hours, allowed to cool, and then filtered. To the filtrate was added 1-bromo-2-fluoroethane (63·5 g., 0·5 mol.), followed by powdered sodium hydroxide (20·0 g., 0·5 mol.), the latter in small portions because a moderate amount of heat was generated by the reaction. The mixture was refluxed for 1½ hours, allowed to cool, and then filtered from a large quantity of organic sulphur-containing impurity. The alcohol was distilled off from the filtrate, under reduced pressure, and the residual liquid was fractionated. A considerable quantity of dithian volatilised over. The liquid displayed no constant b. p., but the fraction, b. p. 139—145°/24 mm., was collected and dried (Na_2SO_4). Further redistillations gave 2 : 2′-difluorodiethyl ethylene dithioglycol ether, b. p. 132—138°/15 mm., free from dithian. The yield was small, and it was evident that this method of preparation was inferior to the previous one.

We wish to thank the Chief Scientist of the Ministry of Supply for permission to publish this paper. We are indebted to Dr. F. J. Buckle who prepared the following compounds: phenyl fluorothiolacetate, 2-chloroethyl fluorothiolacetate, and allyl fluoroacetate.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 15th*, 1948.]

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197. *Organo-lead Compounds. Part I. Trialkyl-lead Salts possessing Sternutatory Properties.*

By B. C. SAUNDERS and G. J. STACEY.

This is the first of a series of papers giving an account of the preparation of organo-lead compounds having powerful sternutatory action. The present paper deals largely with the preparation of salts of the triethyl-, tri-*n*-propyl-, and tri-*n*-butyl-lead series. A definite peak of activity is reached in the tri-*n*-propyl series.

THE work to be described in this series of papers was undertaken in 1939 for the Ministry of Supply, to whom detailed reports were submitted during 1940 and 1941. The original intention was to prepare volatile organic lead compounds of the type PbR_4 (*e.g.*, R = $CH_2{\cdot}CH_2Cl$) which might be toxic by inhalation. At that time, the supplies of arsenic in this country were low, whereas lead was readily available. Tetraethyl-lead was a convenient starting point for such compounds and we accordingly set out to prepare it in quantity from sodium–lead alloy and an ethyl halide. We found, however, that the method described in the patent literature gave poor yields on a laboratory scale. By carrying out a number of experiments, we finally effected the correct modification, which consisted in adding water extremely slowly during the reaction.

The next step was to prepare triethyl-lead chloride in quantity. While working with this compound, one of us (B. C. S.) developed the symptoms of influenza, which, however, wore off at night and returned during the day. The compound was accordingly tested for sternutatory properties and found to give a difficultly respirable atmosphere at a concentration of 1 part in a million. This then gave a great impetus to the preparation of other trialkyl-lead salts. The original intention of preparing substituted plumbanes of the type mentioned above was then dropped and the preparation and examination of trialkyl-lead salts were carried out. Many of these were new compounds and were tested as potential sternutators at Cambridge.

Passing reference had been made by Krause and Pohland (*Ber.*, 1922, **55**, 1282) to the

irritant action of trialkyl-lead fluorides, and Gilman and Robinson (*Rec. Trav. chim.*, 1930, **49**, 766) had noted that sneezing was caused by dust containing traces of triethyl-lead salts. No systematic attempt, however, had been made to correlate potency with the nature of the constituent groupings. It was obviously desirable that this should be undertaken in the hope that it would serve as a guide to the type of compound likely to possess maximum sternutatory action. The work now described was carried out as part of a programme drawn up with this end in view, and attention was directed almost wholly to the preparation of new trialkyl-lead compounds. Emphasis was placed upon the production of substances which had the following characteristics: (i) ease of preparation, (ii) reasonable stability, (iii) strong sternutatory action. Each substance was submitted to physiological examination, the toxicity data being compiled chiefly from the results of human inhalation at known concentrations. The figures so obtained gave a clear indication of the directions in which toxicity increased, and compounds with an action more pronounced than any previously reported in this class were prepared. The most effective compounds did not fall far short of diphenylchloroarsine (D.A.) in potency.

Many of the compounds were easily obtained in a pure condition, were highly crystalline, and have not deteriorated on being stored for a number of years.

Physiological Examination.—Examination of the physiological action upon human beings of these compounds was carried out in a glass-walled chamber of 10 c. m. capacity. The substance was dissolved in a suitable solvent and dispersed in the chamber by means of a spray. Suitably placed fans ensured, as far as possible, an even distribution of the material in the atmosphere inside the chamber. The human observers, four in number, entered the chamber by an air-lock as soon as spraying was complete. The times which then elapsed before irritation occurred in the nose, throat, chest, and gums were noted. Unless the substance proved to be intolerable, the observers stayed in the chamber for 10 minutes. During this period, it was observed that, in spite of all precautions, the activities of some of the compounds decreased because of condensation on the walls of the chamber; hence, it was not always possible accurately to assess the maximum virulence of a compound, especially where this rate of condensation was particularly rapid. Nevertheless, a consistency was almost always obtained among the observations of the four subjects in any one test. From the data thus compiled, a toxicity rating for a given concentration was allotted to each compound on the following basis: Grade 0, not detectable or only slightly irritant; grade 1, unpleasant but tolerable indefinitely; grade 2, very unpleasant but just tolerable indefinitely; grade 3, distressing and not tolerable indefinitely.

The first concentration to be tried was 1 molecule of substance in 10,000,000 molecules of air; *i.e.*, about 20 mg. of organo-lead compound were actually dispersed in the chamber. The required amount was dissolved in about 15 c.c. of solvent (usually alcohol). For certain of the more potent substances, tests were also carried out at concentrations of 1 : 25,000,000.

A list of compounds, whose preparation is described later, is given in the accompanying table, together with their toxicity ratings. These results, taken in conjunction with others

Substance.	1 : 10^7.	1 : 2·5 × 10^7.	Substance.	1 : 10^7.	1 : 2·5 × 10^7.
Triethyl-lead salts.					
Chloride	1	0+	*Anthranilate*	2	—
Acetate	2	1			
Tri-*n*-propyl-lead salts.					
Acetate	3	2+	*Crotonate*	2+	—
Acrylate	2+	1	*Cyanide*	2+	—
Anthranilate	3	2+	*Iodoacetate*	2	—
Bromide	3	1+	*Propionate*	2	—
Bromoacetate	2	—	*Toluene-o-sulphonate*	3	2
n-*Butyrate*	3	2+	*Toluene-p-sulphonate*	3	1+
Chloride	2+	—	*Trichloroacetate*	2	—
Chloroacetate	3	2+	iso*Valerate*	3	1+
β-Chloropropionate	3	—	*Xanthate*	2	—
Tri-*n*-butyl-lead salts.					
Acetate	3	—	*Iodoacetate*	1+	—
Bromoacetate	1+	—	*Naphthalene-β-sulphonate*	2+	—
Chloride	3	—	*Propionate*	2+	—
Chloroacetate	1+	—	*Toluene-p-sulphonate*	2	—
β-Chloropropionate	2+	—	*Trichloroacetate*	2	—
Crotonate	2+	—			

Diethyl-lead dichloride and *bis*-p-*nitrophenoxide*, *di*-n-*propyl-lead dichloride* and *diacetate*, and di-*n*-butyl-lead dichloride at 1 : 10^7 were of grade 0.

obtained for trimethyl-, triethyl-, and tri*iso*butyl-lead compounds (to be described later), show that a definite peak of activity is reached in the tri-*n*-propyl-lead series. The difficulty of obtaining pure compounds prevented extensive work on the diethyl-*n*-butyl-lead series, and tetra*iso*propyl-lead was not sufficiently stable to be of service.

Methods of preparing Trialkyl-lead Salts.—The methods used were all ultimately dependent upon the tetra-alkyl-lead. A very useful method (1), due to Browne and Reid (*J. Amer. Chem. Soc.*, 1927, **49**, 830), consists in warming together a tetra-alkyl-lead and an acid in presence of silica gel. Owing to its directness, this method would no doubt be favoured on a manufacturing scale. We found, however, that it suffers from two main drawbacks: (*a*) it does not proceed easily (especially in the case of the higher alkyls) with weakly acidic substances; (*b*) with too vigorous conditions there is a danger of the formation of the dialkyl-lead salt. This falls into line with Goddard and Goddard's observations (*J.*, 1922, **121**, 973) in the amyl series.

The second general method (2) of preparation consists of the double decomposition of the trialkyl-lead chloride with the appropriate sodium or potassium salt. The removal of any unchanged trialkyl-lead chloride often presents a difficulty here. A useful variation (3) is to use the silver salt, but this is unsuitable for large-scale work.

The method of widest application (4) depends upon the conversion of the tetra-alkyl- into the trialkyl-lead chloride and thence into the hydroxide (Pfeiffer, Truskier, and Disselkamp, *Ber.*, 1916, **49**, 2445; Krause and Pohland, *Ber.*, 1922, **55**, 1282), which on treatment with the appropriate acid gives the required salt. As an extension of this method we have found that, in certain instances, the trialkyl-lead hydroxide will react with the appropriate sodium or potassium salt (5). These methods may be summarised thus:

(1) $PbR_4 + HA \longrightarrow PbR_3A + RH$
(2) $PbR_3Cl + NaA \longrightarrow PbR_3A + NaCl$
(3) $PbR_3Cl + AgA \longrightarrow PbR_3A + AgCl$
(4) $PbR_3OH + HA \longrightarrow PbR_3A + H_2O$
(5) $PbR_3OH + NaA \longrightarrow PbR_3A + NaOH$

Tri-n-*propyl-lead Salts.*—With the discovery that tri-*n*-propyl-lead salts were more powerful sternutators than the corresponding triethyl-lead salts, it became necessary to prepare tetra-*n*-propyl-lead in quantity on a laboratory scale. For this purpose the method generally adopted was the action of sodium–lead alloy on *n*-propyl iodide.

The production of tri-*n*-propyl-lead chloride by the action of hydrogen chloride on tetra-*n*-propyl-lead brought to light several important points. In the first place, this chloride, unlike triethyl-lead chloride, is very soluble in organic solvents (*e.g.*, ether). Consequently, the progress of the reaction could not be judged by the quantity of white crystals formed, and it was necessary to find by trial and error the approximate amount of hydrogen chloride required. After the gas had been passed for some time, a faint white precipitate was formed. This was identified as di-*n*-propyl-lead dichloride, and from this observation a new method for preparing the latter compound was devised (see p. 925). This small amount of precipitate was filtered off, and the ethereal filtrate evaporated, leaving impure tri-*n*-propyl-lead chloride. It was thus found that over-treatment with the gas produced di-*n*-propyl-lead dichloride, and the precipitation of this compound continued even after the actual passage of hydrogen chloride was discontinued. This may have been due to two causes: (i) excess of hydrogen chloride may have reacted slowly with the tri-*n*-propyl-lead chloride first formed: $PbPr_3Cl + HCl = PbPr_2Cl_2 + PrH$; (ii) as shown by Calingaert *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 2748, 3300), triethyl-lead halides can undergo spontaneous and reversible redistribution reactions. Austin (*ibid.*, 1932, **54**, 3287) had shown that this redistribution could be considerably facilitated by heating in benzene or toluene: $2PbEt_3Cl = PbEt_4 + PbEt_2Cl_2$. Similar behaviour will presumably be displayed by the *n*-propyl derivatives, and the direction in which the reaction proceeds will, after a time, be governed by the insolubility of the dichloride. Under the conditions considered above, it is probable that the first reaction is the major one, especially in view of its rapidity and of the good yields of the dichloride obtainable. Thus by passing hydrogen chloride until precipitation had begun, and then allowing the ethereal solution to stand, an almost pure specimen of di-*n*-propyl-lead dichloride was obtained. When preparing tri-*n*-propyl-lead chloride, however, it was found that the use of light petroleum (b. p. 40—60°) (in which the hydrogen chloride is almost insoluble) in place of ether reduced the yield of the dichloride to a minimum. In subsequent preparations, one volume of tetra-*n*-propyl-lead was dissolved in about 10 volumes of this petroleum and a stream of hydrogen chloride was passed through the ice-cooled solution for 2—3 hours. The solvent was rapidly distilled off, and pure tri-*n*-propyl-lead chloride obtained after recrystallisation from aqueous alcohol.

In preparing the tri-*n*-propyl-lead salts the reaction between the hydroxide and the acid in

solution was the most convenient. The tri-*n*-propyl-lead hydroxide was not actually isolated in these preparations, but was prepared in aqueous solution as required. Krause and Pohland (*loc. cit.*) claim to have isolated the compound by treating an ethereal solution of tri-*n*-propyl-lead bromide with aqueous 30% potassium hydroxide. Unlike the ethyl analogue, the tri-*n*-propyl-lead hydroxide was not precipitated, so the ethereal layer had to be separated and the ether removed under reduced pressure, leaving an oily liquid which slowly deposited colourless crystals on standing over quick-lime. The yield was small and the product did not have the m. p. reported by Krause and Pohland. Experiments were then tried, using moist silver oxide as hydrolytic agent. The moist oxide (of known oxide content) was shaken with an aqueous suspension of tri-*n*-propyl-lead chloride in equivalent amount, the precipitate filtered off, and the aqueous solution of the tri-*n*-propyl-lead hydroxide used in further preparative work. The actual amount of hydroxide used was not accurately known, but was estimated on the assumption of a theoretical yield from the chloride. In any case, the amount used need not be accurately established because the procedure was to add sufficient acid to the solution to give a slightly acid reaction to litmus. In this way, the following salts were readily prepared: acetate, acrylate, anthranilate, bromoacetate, bromide, *n*-butyrate, chloroacetate, β-chloro-propionate, crotonate, iodoacetate, *naphthalene-2-sulphonate*, propionate, toluene-*o*- and -*p*-sulphonates, trichloroacetate, and *iso*valerate. Some derivatives, on first being thrown out of solution, did not crystallise readily, but addition of more acid beyond the neutralisation point often facilitated crystallisation. With certain acids, such as acrylic and naphthalene-2-sulphonic, it was necessary to employ alcoholic instead of aqueous solutions. The product was then isolated by evaporation.

The action of an alkali metal on tri-*n*-propyl-lead chloride was used in a few instances where the free acid was not readily available. In this way, the xanthate was prepared and is of interest in that it is an organo-lead compound containing a Pb–S link. The reaction did not proceed to any appreciable extent with sodium or potassium cyanide. In preparing the cyanide, the action of free hydrogen cyanide on tri-*n*-propyl hydroxide was inconvenient, and it was in this connexion that the new method (5) was devised. An aqueous solution of potassium cyanide was added to an aqueous solution of tri-*n*-propyl-lead hydroxide, and tri-*n*-propyl-lead cyanide was readily precipitated.

Results obtained with Dialkyl-lead Salts.—These salts behaved differently from trialkyl compounds and, in particular, their sternutatory powers were negligible (see table).

n-*Butyl Derivatives.*—To determine whether increased physiological activity continued to be displayed as the series was ascended, an investigation of tri-*n*-butyl-lead compounds was undertaken. Tetra-*n*-butyl-lead, first prepared by Danser (*Monatsh.*, 1925, **46**, 241), served as the starting material for these compounds. The pure liquid was obtained by the method recommended by Jones, Evans, Gulwell, and Griffiths (*J.*, 1935, 41) from *n*-butyl magnesium bromide and lead chloride. The product was not distilled before use. It was converted into tri-*n*-butyl-lead chloride by passing hydrogen chloride through a solution of tetra-*n*-butyl-lead in ice-cold light petroleum (b. p. 40—60°) until a precipitate began to form. Pfeiffer, Truskier, and Disselkamp (*loc. cit.*) gave m. p. 109—110° but, in the present work, after three recrystallisations from aqueous alcohol, the m. p. remained at 106·5—108·5°. In general, the material was not recrystallised before use.

Without exception, derivatives were prepared by the interaction of an acid and tri-*n*-butyl-lead hydroxide. It was found that tetra-*n*-butyl-lead reacted much less readily with acids than did tetraethyl-lead.

Results with Tri-n-*butyl-lead Salts.*—The preparation of tri-*n*-butyl-lead hydroxide was attempted in the same manner as for the tri-*n*-propyl compound, but the former substance was not water-soluble, for the aqueous filtrate gave neither precipitates with acids nor an alkaline reaction towards litmus. It was therefore necessary to shake an alcoholic solution of tri-*n*-butyl-lead chloride with moist silver oxide in order to secure a solution of the hydroxide. On adding acids to this solution, the tri-*n*-butyl-lead salts were not, of course, precipitated. Two alternative procedures were available: (i) to evaporate the solution to dryness, leaving the required salt; (ii) to precipitate the salt by addition of excess of water. Except in the case of acetic acid, the second procedure was adopted and found to be satisfactory. In this way, the new tri-*n*-butyl-lead salts recorded in the table were readily obtained.

As several hundred organo-lead compounds were prepared in this series of investigations it was necessary to have a rapid and reliable method of determining lead. Details of the volumetric method employed are given on p. 925.

Experimental.

Sodium–Lead Alloy (22% Na).—Metallic lead (390 g.) was melted in an iron crucible by means of a gas-injector furnace. When the lead was completely molten, dry sodium (110 g., cut into pieces of about 5 g. each) was added, one piece at a time. The lid of the crucible was replaced immediately after each addition so as to keep the violent reaction under control. After all the sodium had been added, the mixture was stirred with an iron rod, the scum removed from the surface, and the molten alloy poured into cylindrical moulds of suitable size.

Tetraethyl-lead.—By following the directions given in *Chemical Reviews*, 1925, **2**, 47 (based on B.P. 216,083), we obtained only traces of tetraethyl-lead. We finally adopted the following conditions. The alloy (400 g.), in small quantities at a time, was ground in a mortar (heat was produced), and transferred as quickly as possible to a 1-l. 3-necked " Quickfit " flask fitted with condenser, dropping-funnel, and stirrer. Ethyl bromide (300 c.c.) was poured on the alloy, pyridine (32 c.c.) was added, and the mixture stirred and heated on a boiling water-bath, a stream of nitrogen being passed through the flask meanwhile. At hourly intervals 2 or 3 drops of water were added. At the end of 8 hours, water was added until no further action took place, and the mass was steam-distilled. The lower layer of the distillate was separated, washed with dilute sodium hydroxide solution, dilute sulphuric acid, and then with water, dried ($CaCl_2$), and distilled; b. p. 83°/13 mm., yield *ca.* 95 g.

Triethyl-lead Chloride.—This was readily obtained from tetraethyl-lead and hydrogen chloride by the method of Gilman and Robinson (*J. Amer. Chem. Soc.*, 1930, **52**, 1975). An improved method of preparation will be given in Part II of this series.

Triethyl-lead Hydroxide.—Triethyl-lead chloride (6·6 g., 0·02 mol.) was added to ether (30 c.c.) in a separating-funnel. Aqueous 30% sodium hydroxide (20 c.c.) was poured in and well shaken. The base was precipitated and rose into the ethereal layer, from which it was filtered off and washed well with ether. During drying, it was kept away from the air as much as possible to minimise reaction with carbon dioxide (cf. Krause and Pohland, *loc. cit.*).

Triethyl-lead Acetate.—Tetraethyl-lead (40 c.c.) and glacial acetic acid (12 c.c.) were heated together under reflux with several pieces of silica gel for 1 hour. The solid which separated was filtered off and washed with a small quantity of cold ether. It had m. p. 160° and was pure (Found: Pb, 58·8. Calc. for $C_8H_{18}O_2Pb$: Pb, 58·7%). It could be recrystallised from benzene, but this was usually unnecessary.

The above reaction is based on that of Browne and Reid (*J. Amer. Chem. Soc.*, 1927, **49**, 836) but we found it necessary to use more nearly molecular proportions (as above) in order to obtain a clean product. Our ratio (vol./vol.) of acetic acid to tetraethyl-lead was 3 : 10, whereas Browne and Reid used 3 : 9 (theoretical, 3 : 10·3).

Triethyl-lead Anthranilate.—To a dilute aqueous solution of triethyl-lead hydroxide was added a cool aqueous solution of anthranilic acid until crystals began to form. An alcoholic solution of anthranilic acid was then added, in small quantities at a time and with much stirring, until the mixture was slightly acid to litmus. The crystals thus obtained were filtered off, washed with water, and dried. The *anthranilate* was recrystallised from light petroleum (b. p. 60—80°) containing 10% of benzene; m. p. 96° (Found: Pb, 48·0. $C_{13}H_{21}O_2NPb$ requires Pb, 48·1%).

Tetra-n-*propyl-lead.*—Lead–sodium alloy containing 78% of lead (265 g., *i.e.*, 1 mol. of lead) was ground to powder and placed in a 1-l. round-bottomed flask fitted with a condenser, stirring rod, and dropping-funnel. *n*-Propyl iodide (453 g., 2·6 mol.) and pyridine (22 c.c.) were poured down the condenser and the whole was stirred on a water-bath, the reactants being kept in an atmosphere of nitrogen. The progress of the reaction was controlled by the addition of 2 c.c. of water every 15 minutes during 5—6 hours. Then more water (about 100 c.c.) was added to decompose the reaction complex. Steam-distillation gave some of the tetrapropyl-lead, which sank to the bottom of the aqueous distillate (about 1500 c.c.) and was separated off, washed with dilute sodium hydroxide solution then dilute sulphuric acid, dried ($CaCl_2$), and filtered. Extraction with ether of the liquid in the reaction flask, followed by washing, drying, and distillation under reduced pressure, gave more of the product of b. p. 80°/0·4 mm.; total yield 113 g. (45% calc. on the *n*-propyl iodide used). The relative amounts obtained by steam-distillation and by ether-extraction varied considerably from one experiment to another. The yield was not appreciably affected by leaving the mixture overnight just before the final addition of water. This compound was first obtained by Grüttner and Krause (*Ber.*, 1916, **49**, 1421) who used the Grignard method.

Tri-n-*propyl-lead Chloride.*—Tetra-*n*-propyl-lead (7·6 g., 0·02 mol.) was dissolved in light petroleum (b. p. 40—60°) (50 c.c.) and a stream of dry hydrogen chloride was passed through until a small quantity of a pinkish-white precipitate appeared. This was filtered off, and the petroleum filtrate quickly evaporated to dryness on the water-bath, and finally under reduced pressure. The product so obtained (6·6 g., 89%) was sufficiently pure for preparation of the hydroxide; it recrystallised from aqueous alcohol in colourless crystals, m. p. 133—134° (Found: Cl, 9·60. Calc. for $C_9H_{21}ClPb$: Cl, 9·54%).

The use of light petroleum (b. p. 40—60°) instead of ether as solvent gives a higher yield with less contamination with di-*n*-propyl-lead dichloride (cf. Pfeiffer *et al.*, *loc. cit.*).

Tri-n-*propyl-lead Hydroxide.*—Moist silver oxide (2·5 g., containing 1·4 g. of oxide, *i.e.*, 0·006 mol.) was mixed with tri-*n*-propyl-lead chloride (1·5 g., 0·004 mol.) in aqueous suspension and the whole was well shaken. The residual solid was removed, giving an aqueous solution of tri-*n*-propyl hydroxide, in which form the reagent was used (cf. *idem*, *ibid.*).

Tri-n-*propyl-lead Acetate.*—To an aqueous solution of tri-*n*-propyl-lead hydroxide was added dilute acetic acid until the liquid was just acid to litmus. A white crystalline precipitate appeared on standing and stirring. The acetate was filtered off, dried, and recrystallised from light petroleum (b. p. 40—60°); m. p. 126—127° (Found: Pb, 52·4. Calc. for $C_{11}H_{24}O_2Pb$: Pb, 52·4%).

Tri-n-*propyl-lead Acrylate.*—An alcoholic solution of tri-*n*-propyl-lead hydroxide was prepared by shaking the chloride in alcohol with freshly prepared moist silver oxide. To the filtrate, an alcoholic solution of acrylic acid was added until the mixture was just acid to litmus. The liquid was evaporated

almost to dryness on the water-bath and the crystals which formed on cooling were filtered off. After thorough draining, the *acrylate* was recrystallised from light petroleum (b. p. 60—80°); m. p. 123° (Found: Pb, 50·5. $C_{12}H_{24}O_2Pb$ requires Pb, 50·8%).

Tri-n-*propyl-lead Bromide*.—An aqueous solution of tri-*n*-propyl-lead hydroxide was added to dilute hydrobromic acid until neutral. After standing for 30 minutes, the precipitate was filtered off, washed well with water, and drained. The sticky solid thus obtained was dried in a desiccator. The solubility in organic solvents was high but it could be recrystallised from a small quantity of light petroleum (b. p. 40—60°); m. p. 76—78° (Found: Pb, 50·1. Calc. for $C_9H_{21}BrPb$: Pb, 49·8%) (cf. Pfeiffer, Truskier, and Disselkamp, *loc. cit.*).

Tri-n-*propyl-lead Bromoacetate*.—Prepared like the acetate, the *bromoacetate* was filtered off after a few minutes' standing, dried, and recrystallised from light petroleum (b. p. 40—60°); m. p. 93—94° (Found: Pb, 42·8. $C_{11}H_{23}O_2BrPb$ requires Pb, 43·7%).

Tri-n-*propyl-lead Anthranilate*.—This *salt* was similarly prepared and recrystallised; m. p. 57—58° (Found: Pb, 43·1. $C_{16}H_{27}O_2NPb$ requires Pb, 43·9%).

By similar means were prepared the n-*butyrate*, m. p. 105—106° (Found: Pb, 48·5. $C_{13}H_{28}O_2Pb$ requires Pb, 48·9%); the *chloroacetate*, m. p. 109—110° (Found: Pb, 48·3. $C_{11}H_{22}O_2ClPb$ requires Pb, 48·2%); the *β-chloropropionate*, m. p. 99—100° (Found: Pb, 46·3. $C_{12}H_{24}O_2ClPb$ requires Pb, 46·7%); the *crotonate*, m. p. 135° (Found: Pb, 48·1. $C_{13}H_{26}O_2Pb$ requires Pb, 49·2%); the *propionate*, m. p. 121—122° (Found: Pb, 50·7. $C_{12}H_{26}O_2Pb$ requires Pb, 50·6%); and the iso*valerate*, m. p. 110—111° (Found: Pb, 47·3. $C_{14}H_{30}O_2Pb$ requires Pb, 47·4%).

Tri-n-*propyl-lead Iodoacetate*.—In this case, the white precipitate produced did not crystallise properly until excess of acid had been added. After standing for a few minutes, the *iodoacetate* was filtered off, dried, and recrystallised as above. The white needles thus obtained soon turned brown on standing; m. p. 88—89° (Found: Pb, 39·8. $C_{11}H_{23}O_2IPb$ requires Pb, 39·8%).

The *trichloroacetate* was prepared and crystallised similarly; m. p. 139—140° (Found: Pb, 41·2. $C_{11}H_{21}O_2Cl_3Pb$ requires Pb, 41·6%).

Tri-n-*propyl-lead Naphthalene*-2-*sulphonate*.—An alcoholic solution of the hydroxide was prepared from moist silver oxide (3 g.) and an alcoholic solution of tri-*n*-propyl-lead chloride (3·7 g., 0·01 mol.). To the filtrate was added an alcoholic solution of naphthalene-2-sulphonic acid (2·1 g., 0·01 mol.) and the mixture was heated on the water-bath for 10 minutes. It was then cooled and excess of water was added with stirring, giving a sticky white precipitate which was kept for a short time before filtration and drying. The *sulphonate* was recrystallised thrice from benzene; m. p. 126—127° (Found: Pb, 35·3. $C_{19}H_{28}O_3SPb$ requires Pb, 38·1%).

Tri-n-*propyl-lead Toluene*-o-*sulphonate*.—To an aqueous solution of tri-*n*-propyl-lead hydroxide, cooled in ice-water, was added, with stirring, an aqueous solution of toluene-*o*-sulphonic acid. At first, an oil separated and, in order to bring about crystallisation, it was necessary to add a slight excess of the acid and to scratch the sides of the vessel vigorously. After standing for a few minutes, the crystals were filtered off, washed with water, and dried. The *toluenesulphonate* was recrystallised from a fairly large quantity of light petroleum (b. p. 40—60°); m. p. 86—87° (Found: Pb, 40·96. $C_{16}H_{28}O_3Pb$ requires Pb, 40·85%).

The *toluene*-p-*sulphonate* was prepared in the same way and its behaviour was very similar; it recrystallised from a large quantity of light petroleum (b. p. 40—60°); crystallisation was slow; m. p. 82—83° (Found: Pb, 40·98%).

Tri-n-*propyl-lead Xanthate*.—To tri-*n*-propyl-lead chloride (3·7 g., 0·01 mol.), dissolved in alcohol, potassium xanthate (1·8 g., 0·011 mol.) was added. The mixture was gently heated under reflux for 20 minutes, cooled, and filtered. On adding water to the filtrate, a brownish, crystalline precipitate was formed. This was filtered off, washed with water and dried. Recrystallisation from light petroleum (b. p. 40—60°), in which it was rather soluble, afforded the *xanthate* as buff-coloured needles on cooling the solution in ice-water; m. p. 57·5° (Found: Pb, 44·7. $C_{12}H_{26}OS_2Pb$ requires Pb, 45·3%).

Tri-n-*propyl-lead Cyanide*.—An aqueous suspension of tri-*n*-propyl-lead chloride (3·7 g., 0·01 mol.) was shaken with moist silver oxide (2·8 g.). To the filtrate was added, with stirring, a dilute aqueous solution of potassium cyanide (1·0 g., 0·015 mol.). The white precipitate which separated was allowed to stand for a short time before being filtered off, drained, and dried. The *cyanide* recrystallised from aqueous alcohol as very fine white needles; m. p. 135° (decomp., after turning brown between 122° and 130°) (Found: Pb, 56·7; CN, 7·66. $C_{10}H_{21}NPb$ requires Pb, 57·2; CN, 7·18%).

Tri-n-*butyl-lead Chloride*.—Tetra-*n*-butyl-lead (Jones, Evans, Gulwell, and Griffiths, *loc. cit.*) (5·4 g., 0·0125 mol.) was dissolved in light petroleum (b. p. 40—60°) (50 c.c.) and dry hydrogen chloride was passed through the ice-cooled solution. A whitish precipitate began to settle out after about 30 minutes and the passage of gas was stopped. The solid was filtered off and the filtrate was evaporated to dryness, leaving a slightly sticky white solid (4·0 g., 77%). Owing to its high solubility in organic solvents, recrystallisation was difficult. Two methods were adopted. One was to dissolve the solid in light petroleum (b. p. 40—60°) and leave the liquid to evaporate slowly. The second, and easier, method was to use aqueous alcohol. After several recrystallisations with the latter solvent, poorly-developed crystals melting to a clear liquid at 106·5—108·5° were obtained (Found: Cl, 8·96. Calc. for $C_{12}H_{27}ClPb$: Cl, 8·57%). In general, the material was not recrystallised before further use.

Tri-n-*butyl-lead Hydroxide*.—Moist silver oxide (2 g., containing 1·2 g. of oxide, *i.e.*, 0·005 mol.) was thoroughly shaken with an alcoholic solution of tri-*n*-butyl-lead chloride (3·3 g., 0·008 mol.). The residual solid was filtered off, and the alcoholic solution of tri-*n*-butyl-lead hydroxide used for the preparation of tri-*n*-butyl-lead salts (cf. Pfeiffer *et al.*, *loc. cit.*).

Tri-n-*butyl-lead Acetate*.—To an alcoholic solution of tri-*n*-butyl-lead hydroxide was added, with stirring, dilute aqueous acetic acid until the mixture was distinctly acid to litmus. The solution was evaporated almost to dryness on the water-bath, and the crystals which formed were drained at the pump and washed with water. After drying, the *acetate* was recrystallised from light petroleum (b. p. 40—60°); m. p. 86° (Found: Pb, 47·4. $C_{14}H_{30}O_2Pb$ requires Pb, 47·4%).

Tri-n-*butyl-lead Bromoacetate*.—A solution was prepared as for the acetate, and addition of excess of

water precipitated the *bromoacetate*. Crystallisation was facilitated by cooling in ice-water and scratching the walls of the vessel. The white solid, after filtration and drying, was extremely soluble in light petroleum and was therefore recrystallised from aqueous alcohol; m. p. 54—55° (Found: Pb, 39·0. $C_{14}H_{29}O_2BrPb$ requires Pb, 40·1%).

Similarly prepared and recrystallised, the *chloroacetate* had m. p. 60° (Found: Pb, 43·4. $C_{14}H_{29}O_2ClPb$ requires Pb, 43·9%); the *crotonate*, m. p. 119° (Found: Pb, 44·8. $C_{16}H_{32}O_2Pb$ requires Pb, 44·7%), and the *iodoacetate*, m. p. 83° (Found: Pb, 36·9. $C_{14}H_{29}O_2IPb$ requires Pb, 36·8%), were crystallised from light petroleum.

Tri-n-butyl-lead β-Chloropropionate.—An alcoholic solution of tri-*n*-butyl-lead hydroxide and dilute aqueous β-chloropropionic acid were mixed and cooled in ice-water; addition of excess of water increased the amount of white precipitate, and after a few minutes this was filtered off and dried. The *β-chloropropionate* was recrystallised from a small volume of light petroleum (b. p. 40—60°), with cooling to 0°; m. p. 65—66° (Found: Pb, 42·5. $C_{15}H_{31}O_2ClPb$ requires Pb, 42·6%).

Tri-n-butyl-lead Naphthalene-2-sulphonate.—Similarly prepared, this *salt* was recrystallised from light petroleum (b. p. 40—60°) containing 10% of benzene; m. p. 68° (Found: Pb, 35·6. $C_{22}H_{34}O_3SPb$ requires Pb, 35·4%).

The toluene-p-sulphonate, similarly prepared and recrystallised, had m. p. 81—82° (Found: Pb, 37·2. $C_{19}H_{34}O_3SPb$ requires Pb, 37·7%).

By a similar method of preparation, the *propionate*, recrystallised from aqueous alcohol, had m. p. 79—80° (Found: Pb, 45·4. $C_{15}H_{32}O_2Pb$ requires Pb, 45·9%), and the *trichloroacetate*, recrystallised from light petroleum (b. p. 40—60°), had m. p. 119° (Found: Pb, 38·1. $C_{14}H_{27}O_2Cl_3Pb$ requires Pb, 38·3%).

Diethyl-lead Dichloride.—Tetraethyl-lead (40·4 g., 0·125 mol.) was dissolved in dry toluene (250 c.c.), and the solution heated on the steam-bath. A stream of dry hydrogen chloride was passed through the liquid, and after a few minutes, a white precipitate began to appear. The passage of gas was continued for twice as long again before the precipitate was filtered off, washed with hot toluene, and thoroughly drained. A further small quantity of solid was obtained by passing hydrogen chloride through the filtrate; yield 31·9 g. (76%). In their original preparation, Gilman and Robinson (*loc. cit.*) claimed a yield of 97% of pure substance. Yakubovich and Petrov (*J. pr. Chem.*, 1936, **144**, 67) stated that considerable quantities of lead chloride and triethyl-lead chloride were also produced, the yield of diethyl-lead dichloride being only 50%.

Diethyl-lead Bis-p-nitrophenoxide.—*p*-Nitrophenol (4·2 g., 0·03 mol.) and tetraethyl-lead (9·7 g., 0·03 mol.) were dissolved in warm xylene, a few pieces of silica gel added, and the whole was gently heated under reflux for 1 hour. A yellow solid separated and was filtered off. It could not be recrystallised from water, ether, benzene, carbon tetrachloride, chloroform, light petroleum, or toluene owing to its insolubility. It was therefore treated with boiling alcohol, filtered off hot, and dried. On heating, the *salt* did not melt, but burnt at a fairly high temperature (Found: Pb, 37·3. $C_{16}H_{18}O_6N_2Pb$ requires Pb, 38·2%).

Di-n-propyl-lead Dichloride.—A slow stream of dry hydrogen chloride was passed through a solution of tetra-*n*-propyl-lead (22·7 g., 0·06 mol.) in absolute ether (150 c.c.) cooled in ice-water. When a faint white precipitate began to appear, the passage of gas was stopped and the liquid was set aside for 24 hours, during which more precipitate slowly formed. This was filtered off and dried, yield, 18·0 g. (82%). The salt was recrystallised from a rather large volume of ethyl alcohol, giving a fine white powder which did not melt below 245° (Found: Cl, 19·5. Calc. for $C_6H_{14}Cl_2Pb$: Cl, 19·5%). (Grüttner and Krause, *Ber.*, 1916, **49**, 1415, used chlorine, instead of hydrogen chloride, in this preparation.)

Di-n-propyl-lead Diacetate.—Moist silver oxide (5·1 g., containing 50% of water) was shaken with an aqueous suspension of di-*n*-propyl-lead dichloride (3·6 g., 0·01 mol.). The solid was filtered off, and the aqueous solution of di-*n*-propyl-lead dihydroxide thus obtained was used in the following preparation. To this solution was added dilute aqueous acetic acid until the mixture was acid to litmus. The solution was allowed to evaporate over sulphuric acid in an evacuated desiccator. The sticky residue thus obtained was drained, dried, and recrystallised from light petroleum (b. p. 60—80°), giving the *diacetate*, m. p. 122° (decomp.) (Found: Pb, 49·7. $C_{10}H_{20}O_4Pb$ requires Pb, 50·4%); mixed m. p. with an equal quantity of tri-*n*-propyl-lead acetate, 104—114°.

Determination of Lead in an Organic Compound.—The compound (0·15—0·2 g.) was digested with concentrated nitric acid on a hot plate until all the oxides of nitrogen ceased to be evolved (complete removal of these oxides was essential). To the precipitated lead nitrate, water (100 c.c.) was added, followed by 4N-ammonia solution until all the plumbous hydroxide had been precipitated. Aqueous acetic acid (10%) was then added until a clear solution was obtained, and this was heated to 90°. Potassium dichromate solution (approx. 1%) was added from a burette, about 2 c.c. at a time, with shaking and reheating after each addition. When no more precipitate was formed and coagulation was complete, a 25% excess of the dichromate solution was added, and the mixture heated on a hot plate for 15 minutes with constant shaking. If the supernatant liquid was then not quite clear, a further 2 c.c. of dichromate was added, and the heating repeated.

The precipitate of lead chromate was collected on a Swedish filter-paper and washed with warm 5% ammonium acetate solution. The filter paper was pierced, and the precipitate washed with warm dilute hydrochloric acid into a conical flask. The solution was then cooled and titrated with approx. N/10-ferrous ammonium sulphate solution, ferrous phenanthroline being used as internal indicator. One minute was allowed for fading when determining the end-point. The ferrous ammonium sulphate solution was standardised against pure lead nitrate.

We thank the Chief Scientist of the Ministry of Supply for permission to publish the above, and we express our gratitude to Mr. F. E. Smith who carried out numerous lead analyses. We wish to thank Dr. B. A. Kilby for supervising the majority of the inhalation experiments.

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198. *A Kinetic Study of the Hydrolysis of Diisopropyl Fluorophosphonate.*

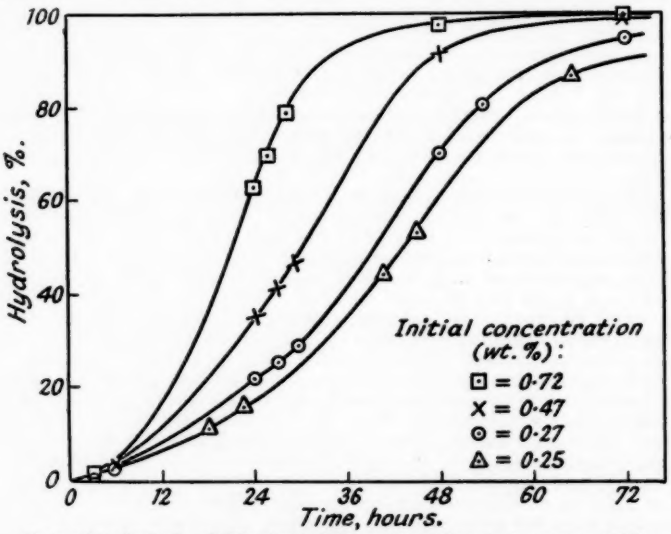
By William A. Waters and C. G. M. de Worms.

The hydrolysis of di*iso*propyl fluorophosphonate in neutral or acid solution yields hydrogen fluoride and di*iso*propyl phosphate. The reaction is catalysed by hydrogen ions, and therefore differs in mechanism from the hydrolysis of acyl chlorides, R·COCl.

The physiologically active liquid di*iso*propyl fluorophosphonate (McCombie and Saunders, *Nature*, 1946, **157**, 287, 776; Saunders and Stacey, *J.*, 1948, 695) is hydrolysed slowly in water, and rapidly in dilute alkali, to innocuous products. Information concerning these reactions is therefore of some pharmacological interest and the studies which are described below were originally carried out for this reason, though they have a theoretical value which deserves comment. Preliminary investigations showed that the rate-determining process is the separation of fluoride anions (1), though subsequently reaction (2) may occur at a rate which, however, is never more than 5% of (1).

$$(1)\ (C_3H_7\cdot O)_2POF + H_2O \longrightarrow (C_3H_7O)_2PO\cdot OH + HF$$
$$(2)\ (C_3H_7\cdot O)_2PO\cdot OH + H_2O \longrightarrow (C_3H_7O)PO(OH)_2 + C_3H_7\cdot OH$$

The course of the reaction can be followed quite easily at 25° by withdrawing at intervals aliquot parts of solutions of the fluorophosphonate and titrating each sample (*a*) for free acid, using sodium hydroxide and phenolphthalein, and then (*b*) for fluoride ion, using thorium nitrate



Rate of hydrolysis of diisopropyl fluorophosphonate in water at 25°.

(Milton, Liddell, and Chivers, *Analyst*, 1947, **72**, 43; compare *ibid.*, 1944, **69**, 243). Since titration (*b*) is carried out in acid solution the presence of phenolphthalein causes no interference. At first, difficulties due to the reaction of hydrogen fluoride with glass containing vessels were encountered, but they were overcome by the use of copper vessels which had been coated with water-resistant bakelite enamel (Ministry of Supply Specification CD 3). The dissolution of the di*iso*propyl fluorophosphonate could be assisted by the addition of up to 5% of ethyl alcohol without there being any detectable change in the hydrolysis rate. Since the buffering actions of phosphoric acid, and its acid esters, reduce the accuracy of the sodium hydroxide titrations in the later stages of the hydrolysis, the reaction-velocity constants were always computed from the fluoride titres, which were always highly sensitive and reproducible.

The figure shows that the hydrolysis of di*iso*propyl fluorophosphonate in water at 25° is an autocatalytic process, and that decomposition is substantially complete in 3 days.

The hydrolysis is evidently a process which is catalysed by hydrogen ions, for the initial rate of hydrolysis, *i.e.*, 0·6% per hour, is independent of the initial concentration of the fluorophosphonate. To confirm this, measurements were carried out in the presence of a sufficient

concentration of hydrochloric acid to keep the pH of the solution reasonably constant, and also in a solution buffered to pH 3·0 by a chloroacetic acid–sodium chloroacetate mixture. Under these conditions, too, the rate of liberation of fluoride anions was of first order (see Experimental). A check experiment showed that the rate of hydrolysis in 1% sodium chloride solution was the same as in distilled water, so that evidently the catalysis is due to hydrogen ions and not to chloride anions also. Table I lists the results obtained.

TABLE I.

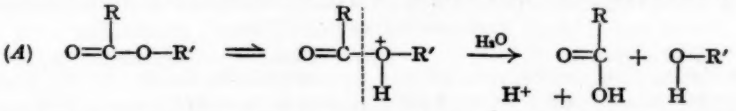
Rate of hydrolysis of diisopropyl fluorophosphonate at 25° (time in hours).

At pH = 7 : k = 0·006	initial rate in water
pH = 3·0 : k = 0·0122	in chloroacetate buffer
pH = 1·7 : k = 0·102	in 0·02N-hydrochloric acid
pH = 1·3 : k = 0·225	in 0·05N-hydrochloric acid

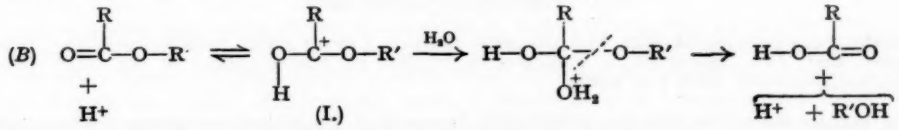
In alkaline solution di*iso*propyl fluorophosphonate hydrolyses very rapidly indeed. With equivalent concentrations corresponding to equation (3) the liberation of fluoride anion is complete in about 15 minutes at 25° (compare Saunders and Stacey *loc. cit.*) :

(3) $(C_3H_7{\cdot}O)_2POF + 2NaOH = (C_3H_7O)_2PO{\cdot}ONa + NaF + H_2O$

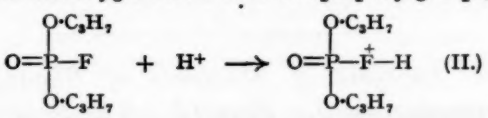
Discussion.—Since the hydrolysis of di*iso*propyl fluorophosphonate is an acid-catalysed process, the rate-determining stage cannot be the direct heterolysis of the P–F link. Thus although it resembles an acyl halide it behaves in a very different manner from the acyl chlorides which undergo simple unimolecular (S_N1) hydrolysis (compare Berger and Olivier, *Rec. Trav. chim.*, 1927, **46**, 861). Acid-catalysed hydrolysis, however, occurs in esters, $R{\cdot}CO_2R'$, and in ortho-esters, $R{\cdot}C(OR')_3$. It is usually ascribed to a proton attack on the alkyloxy-group which brings about a weakening of the C–O link sufficient for the rapid solvolysis of the molecule-ion complex (Mechanism *A* ; compare Lowry, *J.*, 1925, **127**, 1380; Waters, *J.*, 1936, 1014; Day



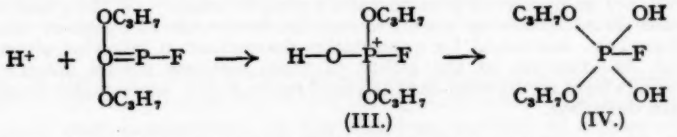
and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686) rather than attack at the C=O group (mechanism *B* ; compare Watson, " Modern Theories of Organic Chemistry," 1937, p. 130) since this cannot occur with the ortho-esters.



With di*iso*propyl fluorophosphonate, the process which is equivalent to (*A*) would involve the fluorine atom rather than the oxygen atoms of the *iso*propoxy-groups, *i.e.* :



The breakdown of (II) would have to be a solvolysis by water acting as a nucleophilic reagent, and attacking the phosphorus atom of the *weakly* polar P=O group and not the positively charged fluorine atom. A justification of the bicovalency of fluorine in (II) would be extremely difficult. The alternative mechanism of proton attack on the oxygen atom of the double bond is, in this case, much more probable : it would lead to the formation of a phosphonium kation



(III) in which the positively charged phosphorus atom might well be able to abstract a hydroxyl anion from a water molecule so as to yield a quinquecovalent complex (IV), structurally analogous

to phosphorus pentafluoride. Thereupon the loss of hydrogen fluoride regenerates anew the P=O double bond in di*iso*propyl phosphate.

Although a firm decision in favour of this second mechanism for the hydrolysis of the fluorophosphonate is impossible upon the scant evidence now available, yet it is clear that the mechanisms of reactions of compounds of phosphorus, and of fluorine, cannot safely be inferred from consideration of similar compounds of carbon and chlorine. The essential differences may be due to (i) the different electronic structures of C=O and P=O linkages, in the latter of which *d* electrons are concerned, and (ii) a marked difference in the partial ionic characters of P–F and C–Cl covalencies. In this latter connection, a kinetic study of the hydrolysis of acyl fluorides would be of great interest.

Experimental.

The di*iso*propyl fluorophosphonate was purified by repeated distillation under reduced pressure (b. p. 68°/9 mm.) and had 100% purity as determined by fluorine content. After storage for 5 weeks in a dry glass bottle the purity had fallen to 97%. Samples were weighed into graduated flasks, dissolved in a few ml. of ethyl alcohol, and then diluted with distilled water and, after thorough mixing, transferred to bakelite-enamel-coated copper vessels immersed in a thermostat at 25°. Since the solubility of di*iso*propyl fluorophosphonate is 1·54% at 25° (Ministry of Supply Report), concentrations of up to 0·8% could be handled without difficulty. Table II shows typical results of titration (i) with sodium

Table II.

Hydrolysis of a 0·37% solution in water at 25° (enamelled vessel).

Time (hours)	3	5	24	28	47	49	53	71
Hydrolysis, % (method i)	1·34	2·19	17·5	22·0	52·4	54·9	61·4	77·7
,, (method ii)	1·43	2·00	15·6	20·2	50·1	51·8	58·0	71·7

Table III.

Hydrolysis of diisopropyl fluorophosphonate in 0·02N-hydrochloric acid (in glass) at 25°: Initial concentration = 0·0309M.

Time (hours).	Hydrolysis, %. By NaOH.	By $Th(NO_3)_4$.	*k*.*	Time (hours).	Hydrolysis, %. By NaOH.	By $Th(NO_3)_4$.	*k*.*
0·5	4·9	4·8	0·119	4·5	40·6	37·0	0·104
1·0	9·4	10·2	0·108	5·0	41·4	38·8	0·099
2·3	20·8	20·5	0·099	5·0	45·5	45·0	0·109
3·0	26·0	24·9	0·095	6·0	47·9	46·0	
3·5	31·2	30·0	0·101				Mean 0·102

* From thorium nitrate titres.

hydroxide using phenolphthalein, and (ii) with thorium nitrate using Solochrome-blue. Table III indicates that the hydrolysis is pseudo-unimolecular in the presence of an acid catalyst: $k = (1/t)\log_e a/(a - x)$, with t in hours.

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C.D.E.S., Porton, Wilts. (Ministry of Supply.) [*Received, September 17th*, 1948.]

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199. *Quantitative Analysis of Mixtures of Sugars by the Method of Partition Chromatography. Part II. The Separation and Determination of Methylated Aldoses.*

By E. L. Hirst, L. Hough, and J. K. N. Jones.

(*a*) Methylated derivatives of reducing sugars can be separated by the method of paper partition chromatography, and this method has been used for the identification of the sugar derivatives produced on hydrolysis of methylated polysaccharides. (*b*) The quantitative determination of methylated aldoses on the micro-scale has been achieved by use of alkaline iodine, and a method has been elaborated for quantitative determination following chromatographic separation. (*c*) As examples of the utility of these methods results obtained with the hydrolysis products from methylated derivatives of maize starch, waxy-maize starch, glycogen, and araban are described.

In Part I (Flood, Hirst, and Jones, *J.*, 1948, 1679) chromatographic separations of reducing sugars and their subsequent determination by use of Somogyi's copper reagent were described.

An extension of this work to the methylated sugars has now shown that the partition method of chromatography using filter-paper is exceedingly sensitive in that it allows of the separation of closely related methylated sugar derivatives. For example, 2 : 4 : 6-trimethyl glucose can be identified in the presence of 2 : 3 : 6-trimethyl glucose, and 2 : 3-dimethyl xylose can be readily separated from 2 : 4-dimethyl xylose (Brown, Hirst, Hough, Jones, and Wadman, *Nature*, 1948, **161**, 720).

This method of separation provides a semimicro-procedure for the rapid identification of the methylated sugars liberated by hydrolysis of methylated polysaccharides. 2 : 3 : 4 : 6-Tetramethyl D-glucose is used as a standard reference substance and the ratio between the distance the sugar derivative travels to the distance through which tetramethyl D-glucose has moved gives a constant (R_G) characteristic of the sugar (see Table I). When a mixture of sugars is separated in this way the R_G values give indications of the identity of the components, but it must be remembered that the formation of a single spot on the paper chromatogram is not a complete proof of the homogeneity of the sugar since a number of the methylated sugars possess similar R_G values.

In order to test the usefulness of the new method, an examination was made of the products of hydrolysis of the methylated derivatives of maize starch, waxy maize starch, glycogen, sugar-beet araban, and peanut araban. The presence of all of the methylated sugars previously isolated by fractional distillation of the mixed glycosides was readily established and indications were obtained of the presence of traces of other partly methylated sugars. The latter originated in all probability from slight under methylation of the product submitted to hydrolysis, but the method is so sensitive that products due to the very slight demethylation of methylated sugars by methanolic hydrogen chloride would be detectable despite the minute proportions in which they occur.

These results, although highly useful, are qualitative only, but if a suitable reagent could be found for the determination of methylated derivatives of reducing sugars it would be possible to separate chromatographically and determine quantitatively the sugars produced on hydrolysis of small amounts of methylated polysaccharides. It was soon found, in agreement with other workers, that copper reagents are not entirely satisfactory for the determination of the methylated sugars. Sobotka (*J. Biol. Chem.*, 1926, **69**, 297) and Jeanloz (*Helv. Chim. Acta*, 1946, **29**, 57) have demonstrated, however, that alkaline iodine can be used for the determination of methylated aldoses, and we have adapted this method for the micro-determination of reducing methylated aldoses. The procedure for the separation and extraction of the methylated sugars is identical with that previously described for the estimation of the non-substituted reducing sugars (Part I, *loc. cit.*). In contrast with the non-substituted sugars, the methylated derivatives show a wide spatial separation on the chromatogram and comparatively large quantities of the sugars can, therefore, be separated, the process of determination being thereby simplified. The sugar extracted from the filter paper is determined by oxidation with 0·1N-iodine solution, introduced from an " Agla " micrometer syringe, in the presence of a sodium carbonate–sodium bicarbonate buffer (pH 10·6). Blank experiments have shown that 0·5—3·0 mg. of methylated sugar can be determined with an accuracy of $\pm 8\%$ and that the recovery of the methylated sugars from the paper chromatogram is of the order of 96%. As examples of the utility of this procedure we record the results obtained with (*a*) a synthetic mixture of 2 : 3 : 4 : 6-tetramethyl D-glucose, 2 : 4 : 6-trimethyl D-glucose, and 2 : 4-dimethyl D-galactose, and (*b*) a mixture of 2 : 3 : 4-trimethyl D-xylose, 2 : 4-dimethyl D-xylose, 2 : 4-dimethyl D-galactose, and L-rhamnose (see Experimental section).

The unsubstituted pentose and hexose sugars can also be determined by alkaline hypoiodite under carefully controlled conditions of alkalinity (Hawthorne, *Nature*, 1947, **160**, 714), but in agreement with Myrbäck (*Svensk Kem. Tids.*, 1940, **52**, 293) we find that this reagent is unsatisfactory for the determination of D-mannose. L-Rhamnose, D-lyxose, and D-talose are also incompletely oxidised under these conditions. Nevertheless, D-ribose, which has the same configuration of hydroxyl groups on C_2 and C_3 as these sugars, may be determined satisfactorily. Mannose, rhamnose, lyxose, and talose can be satisfactorily determined, however, if a control determination is carried out simultaneously with the determination of the sugar, and the appropriate correction made.

As test cases for the application of the quantitative procedure to methylated polysaccharides we selected methylated waxy-maize starch and methylated rabbit-liver glycogen, using samples which had already been investigated by the standard method of methanolysis followed by fractional distillation. In both cases no less than five methylated derivatives of glucose were found chromatographically after hydrolysis. The separated sugars were determined by

oxidation with alkaline hypoiodite. The hydrolysis products from methylated waxy-maize starch had the following percentage composition: 2 : 3 : 4 : 6-tetramethyl glucose (4·2%), 2 : 3 : 6-trimethyl glucose (80%), 2 : 3-dimethyl glucose (3%), a dimethyl glucose (11%) (not previously observed; identity uncertain), and a monomethyl sugar (2%). This sample of methylated waxy-maize starch had been examined previously by Dr. T. G. Halsall by the standard procedure and the yield of tetramethyl D-glucose was 4·4%. The yield by the present method is 4·6% calculated on the weight of polysaccharide hydrolysed, and is, therefore, in good agreement with the earlier value. This applies also to the methylated glycogen, the hydrolysis products from which contained 2 : 3 : 4 : 6-tetramethyl glucose (8·5%, equivalent to 9·2% on the weight of polysaccharides), 2 : 3 : 6-trimethyl glucose (70%), 2 : 3-dimethyl glucose (9%), a dimethyl glucose (10·6%) (not previously observed; identity uncertain), and a monomethyl derivative (2·5%). This methylated glycogen, when examined by the method of methanolysis and fractional distillation had given 9% of tetramethyl glucose. A comparison of the yields of the other sugars, both from waxy-maize starch and from glycogen is not possible since reliable methods of estimation have not hitherto been available. It is of interest to note that Freudenberg and Boppel (*Ber.*, 1940, **73**, 609) found two kinds of dimethyl glucose amongst the hydrolysis products of a sample of methylated starch. The structural significance of this is, however, uncertain since some of the dimethyl glucose and probably all of the monomethyl glucose may be ascribable to the incomplete state of methylation of the polysaccharides (OMe, 43% instead of 45·6%). The new method would detect also any products resulting from the demethylation of methylated sugars by the hydrochloric acid used for the hydrolysis. In the present instances, however, these latter effects are of negligible importance.

Experimental.

(1) *Qualitative.—The chromatographic separation of methylated derivatives of sugars.* The apparatus and solvents used were similar to those described previously (Partridge, *Nature*, 1946, **158**, 270; *Biochem. J.*, 1948, **42**, 238; Flood, Hirst, and Jones, *loc. cit.*). With the aid of a capillary tube a small spot of solution containing the sugars under investigation is placed on the starting line of the paper (15 × 50 cm.). Alongside this spot and at a distance of about 3 cm. is placed a small spot of a 10% aqueous solution of tetramethyl D-glucose. The experiment is allowed to run until the solvent [the top layer of a mixture of *n*-butanol (40%), ethanol (10%), water (49%), and ammonia (1%)] is approximately 40 cm. from the starting line on the paper. The paper then is removed, dried, and sprayed with an ammoniacal solution of silver nitrate (10%); on heating, the positions of the separated sugars are indicated by brown spots. The R_G values of the separated sugars are calculated from the ratio between

Table I.

Substance.	R_G.	Substance.	R_G.
1. Galactose	0·08	32. 4-Methyl rhamnose	0·57
2. Glucose	0·09	33. 3 : 4-Dimethyl mannose	0·58
3. Sorbose	0·11	34. Glucomethylose 3-methyl ether	0·60
4. Mannose	0·12	35. 2-Deoxyrhamnose	0·61
5. Fructose, Tagatose	0·13	36. 2 : 3-Dimethyl arabinose	0·63
6. Arabinose	0·14	37. 2 : 3 : 4-Trimethyl galactose	0·64
7. Xylose	0·15	38. 2 : 4-Dimethyl xylose	0·66
8. 4-Methyl galactose	0·17	39. 3 : 4-Dimethyl fructose	0·66
9. 6-Methyl galactose	0·19	40. 2 : 4 : 6-Trimethyl galactose	0·67
10. Talose, Lyxose	0·19	41. Altromethylose 3-methyl ether	0·68
11. 2-Methyl galactose	0·21	42. 2 : 3 : 6-Trimethyl galactose	0·71
12. Ribose, Fucose	0·21	43. 2 : 3-Dimethyl xylose	0·74
13. Riboketose	0·25	44. 2 : 4 : 6-Trimethyl glucose	0·76
14. 3-Methyl glucose	0·27	45. 3 : 4 : 6-Trimethyl mannose	0·80
15. Xyloketose	0·26	46. 2 : 3 : 6-Trimethyl glucose	0·81
16. 6-Methyl glucose	0·27	47. 2 : 3 : 6-Trimethyl mannose	0·81
17. Quinovose (glucomethylose)	0·28	48. 1 : 3 : 4-Trimethyl fructose	0·84
18. Rhamnose	0·30	49. Cymarose	0·87
19. 3 : 4-Dimethyl galactose	0·32	50. 2 : 3 : 4 : 6-Tetramethyl galactose	0·88
20. 2-Deoxyallose	0·33	51. Oleandrose	0·88
21. 2-Methyl arabinose	0·36	52. 3 : 4-Dimethyl rhamnose	0·88
22. 3 : 6-Anhydroglucose	0·37	53. 1 : 3 : 4 : 5-Tetramethyl fructose	0·90
23. Rhamnoketose	0·37	54. 2 : 3 : 4-Trimethyl xylose	0·94
24. 2-Methyl xylose	0·39	55. 2 : 3 : 5-Trimethyl arabinose	0·95
25. 2 : 4-Dimethyl galactose	0·41	56. 2 : 3 : 4 : 6-Tetramethyl mannose	0·96
26. 4 : 6-Dimethyl glucose	0·46	57. 2 : 3 : 4 : 6-Tetramethyl glucose	1·0
27. 2 : 6-Dimethyl galactose	0·49	58. 2 : 3 : 4-Trimethyl rhamnose	1·01
28. 2-Methyl fucose	0·51	59. Raffinose	No movement
29. 3 : 6-Dimethyl glucose	0·51	60. Sucrose	0·04
30. 2 : 3-Dimethyl mannose	0·54	61. β-Methyl arabopyranoside	0·33
31. 2 : 3-Dimethyl glucose	0·57	62. α-Methyl mannopyranoside	0·30

the distance from the starting line to the centre of the spot and the distance through which the tetramethyl D-glucose has moved. Table I gives the R_G values of a variety of methylated sugars determined by this procedure. The values for a number of non-reducing sugars have also been determined by spraying the chromatogram with a solution of naphtharesorcinol in alcoholic hydrogen chloride (Forsyth, *Nature*, 1948, **161**, 239).

The examination of a methylated polysaccharide by this procedure is conveniently carried out with approximately 50 mg. of material which is hydrolysed with 4% methanolic hydrogen chloride (1 ml.) in a sealed tube immersed in a boiling water-bath. After hydrolysis the tube and its contents are cooled, and the tube opened cautiously. An aqueous solution of hydrochloric acid (4%; 5 ml.) is then added and the methyl glycosides are hydrolysed at 100° for 3 hours. The solution is then neutralised with silver carbonate, filtered, and the silver is removed by passage of hydrogen sulphide. After filtration, acidic materials and uronic acid derivatives are removed by the use of Amberlite Resin, IR4B, and the neutral solution evaporated to a thin syrup which is examined on the paper chromatogram. The R_G values of the separated components give an indication of identity, and further evidence is obtained by comparison on another chromatogram with an artificial mixture of the suspected sugars. Table II gives the results of the application of this procedure to some methylated polysaccharides which have previously been examined by the method of methanolysis followed by fractional distillation of the methylated methyl glycosides.

TABLE II.

Methylated polysaccharide.	R_G *Values of the separated sugars.*
Maize starch Waxy-maize starch Glycogen	1·00(57)*; 0·805(46)*; 0·57(31)*; 0·51†; 0·26†
Sugar-beet araban Peanut araban	0·95(55)*; 0·635(36)*; 0·37(21)*; 0·27‡; 0·11‡

The numbers in parentheses are those of the sugar concerned as listed in Table I.
* Previously observed by fractional distillation method.
† Not previously observed; identity uncertain.
‡ In small amount; not previously observed; identity uncertain.

TABLE III.

Substance.	Amount weighed out (mg.).	Found by titration (mg.).	Recovery, %.
L-Arabinose	1·03	1·03	100
,,	2·06	2·06	100
,,	3·09	3·07	99·5
D-Galactose	0·565	0·56	99
,,	1·13	1·13	100
,,	2·26	2·22	98
,,	2·82	2·78	98·5
D-Ribose	0·565	0·56	99
,,	1·13	1·13	100
,,	2·22	2·26	101·5
,,	2·78	2·82	101·5
D-Xylose	1·60	1·58	98·5
,,	3·20	3·16	98·5
D-Lyxose	1·18	1·06	90
D-Mannose	0·51	0·48	94
,,	1·02	0·92	90
,,	2·04	1·64	80·5
L-Rhamnose	0·97	0·87	89·5
,,	1·94	1·64	84·5
,,	2·91	2·11	72·5
D-Talose	1·26	1·17	93
2 : 4-Dimethyl D-xylose	0·475	0·49	103
,, ,,	0·95	0·935	98·5
,, ,,	1·225	1·29	105
2 : 4 : 6-Trimethyl D-glucose	0·40	0·415	104
,, ,,	0·80	0·75	94
,, ,,	1·20	1·22	101·5
,, ,,	1·60	1·58	99
2 : 3 : 6-Trimethyl D-glucose	0·555	0·53	96
,, ,,	1·105	1·065	97
,, ,,	2·21	2·20	99·5
2 : 3 : 4 : 6-Tetramethyl D-glucose	1·36	1·37	100·5
,, ,,	2·04	2·00	98
,, ,,	2·38	2·52	106

(2) *Quantitative.—Micro-determination of the aldoses and their methylated derivatives using sodium hypoiodite.* A 0·1N-solution of iodine (1 ml.) is added from an " Agla " micrometer syringe to the sugar solution (5 ml.) (which should not contain more than 2·5 mg. of sugar; otherwise oxidation will be incomplete) contained in a boiling tube (22 × 3 cm.) fitted with a B24 ground-glass stopper. A solution (2 ml.) containing 0·2M-sodium hydrogen carbonate and 0·2M-sodium carbonate (pH 10·6) is then pipetted

into the solution, and the tube stoppered. In order to prevent loss of iodine due to evaporation, the stopper is moistened with a little potassium iodide solution (10%). A control determination is carried out on 5 ml. of water contained in a similar boiling tube. After 2—2½ hours the stopper is washed, and the reaction mixture diluted to 25 ml. and then acidified by carefully running 2N-sulphuric acid down the side of the tube and avoiding unduly vigorous evolution of carbon dioxide. After acidification the tube is stoppered pending titration of the liberated iodine with 0·01N-sodium thiosulphate solution.

The method is satisfactory for the determination of glucose, galactose, arabinose, xylose, ribose, and their methylated derivatives, but with the rhamnose, lyxose, talose, and mannose theoretical values were not obtained for the unmethylated sugars. For the quantitative determination of these a standard aqueous solution of the particular sugar is analysed simultaneously, its concentration being adjusted so that 5 ml. will contain approximately the same quantity of sugar as is to be analysed. In this way an accurate determination of these four sugars can be achieved, or alternatively, the determination may be carried out by reference to a correction curve calibrated for each individual sugar.

Typical results are shown in Table III. In several instances figures are given for a series of analyses which show how the method responds to varying amounts of the sugar which is being determined.

The Determination of the Aldoses and their Methylated Derivatives after Chromatographic Separation.—In order to obtain measurable quantities of the separated sugars the method of Flood, Hirst, and Jones (*loc. cit.*) is used. The filter-paper strips thus obtained are extracted for ½ hour with 5 ml. of water contained in a boiling-tube. The sugar solution is then cooled to 20° and analysed by the method described above.

Substance.	Quantity used (mg.).	Found by titration (mg.). Expt. 1.	Expt. 2.	Calc. from reference compound (mg.). Expt. 1.	Expt. 2.	Average recovery, %.
(*a*) *Analysis of a mixture of* D-*galactose and* L-*arabinose using* D-*ribose as the reference sugar* (*for details of method see Part I*):						
D-Galactose	7·16	1·08	1·24	7·10	7·19	100
L-Arabinose	3·66	0·60	0·685	3·95	3·96	108
D-Ribose	5·24	0·795	0·905	—	—	100 (Ref. substance)
(*b*) *Analysis of a mixture of* 2 : 3 : 4 : 6-*tetramethyl* D-*glucose and* 2 : 4-*dimethyl* D-*galactose using* 2 : 4 : 6-*trimethyl* D-*glucose as the reference sugar*:						
2 : 3 : 4 : 6-Tetramethyl D-glucose	28·93	2·77	3·45	26·8	26·3	92
2 : 4 : 6-Trimethyl D-glucose	23·16	2·43	3·04	—	—	100 (Ref. substance)
2 : 4-Dimethyl D-galactose	12·86	1·24	1·55	12·8	12·8	100
(*c*) *Analysis of a mixture of* 2 : 3 : 4-*trimethyl* D-*xylose*, 2 : 4-*dimethyl* D-*galactose*, and L-*rhamnose using* 2 : 4-*dimethyl* D-*xylose as the reference sugar*:						
2 : 3 : 4-Trimethyl D-xylose	11·63	1·42	1·47	12·4	13·0	109
2 : 4-Dimethyl D-xylose	31·93	3·66	3·60	—	—	(100 Ref. substance)
2 : 4-Dimethyl D-galactose	22·63	2·34	2·18	22·2	21·0	96
L-Rhamnose	16·18	1·75	1·85	15·3	16·4	98

(*d*) *Examination of methylated waxy-maize starch.* The material used had OMe, 43·2%. The methylated polysaccharide (50 mg.) was hydrolysed with 4% methanolic hydrogen chloride (1 c.c.) in a sealed tube at 100°, and the resultant glycosides hydrolysed (7 hours) as described above. The methylated sugars were chromatographically separated and determined by the hypoiodite method.

R_G of sugar derivative.	Derivative of glucose indicated.	Found (mg.).	Composition, %.
1·00	2 : 3 : 4 : 6-Tetramethyl	0·28	4·2
0·81	2 : 3 : 6-Trimethyl	5·37	80·0
0·58	2 : 3-Dimethyl	0·27	4·0
0·51	3 : 6-Dimethyl	0·70	10·4
0·26	Monomethyl	0·09	1·3

(*e*) *Examination of methylated rabbit-liver glycogen.* The methylated polysaccharide (50 mg.) was hydrolysed and portions of the resultant methylated sugars were separated and determined by the method of paper partition chromatography.

R_G of sugar derivative.	Derivative of glucose indicated.	Found (mg.).	Composition, %.
1·00	2 : 3 : 4 : 6-Tetramethyl	0·14	8·7
0·81	2 : 3 : 6-Trimethyl	1·13	69·0
0·58	2 : 3-Dimethyl	0·15	8·9
0·51	3 : 6-Dimethyl	0·18	10·8
0·26	Monomethyl	0·04	2·4

The authors wish to thank Dr. D. J. Bell, Dr. T. G. Halsall, Dr. E. G. V. Percival, and Professor T. Reichstein for gifts of materials, and the Department of Scientific and Industrial Research for a grant awarded to one of them (L. H.).

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200. *The Kinetics of Aromatic Halogen Substitution. Part VI. Iodine-catalysed Bromination.*

By P. W. ROBERTSON, J. E. ALLAN, K. N. HALDANE, and (MISS) M. G. SIMMERS.

The iodine-catalysed bromination of hydrocarbons such as mesitylene in carbon tetrachloride solution proceeds by simultaneous reactions, of different order with respect to iodine for the same bromine concentration. There are maximum rates with added iodine, and a graphical interpretation shows that the positions of the maxima correspond with those required for the proposed simultaneous reactions. The rate measurements by Bruner (1902) for the iodine-catalysed bromination of benzene are also analysed by this method. Theoretical considerations indicate that the experimental results are consistent with a reaction proceeding in two stages, in each of which the iodine, as either its tribromide or its bromide, may participate.

THE efficiency of iodine as a catalyst in bromine substitution has long been known, and the first to make a kinetic study of the reaction was Bruner (*Z. physikal. Chem.*, 1902, **41**, 514). He examined especially the bromination of benzene, without the addition of a solvent, varying the amounts of bromine and iodine. The results corresponded with fourth-order kinetics, *i.e.*, for the total halogen, and approximately bimolecular rates were found for the individual runs. Bruner endeavoured to explain these results by a theory involving formation of bromine atoms from iodine bromide, but it was not indicated how the proposed mechanism accorded with other characteristics of the reaction, the maximum velocity with added iodine, and the rapid fall in rate in the individual reactions when the amount of iodine was considerable.

A further investigation of the nature of the iodine catalysis of bromination was made by Price, who used phenanthrene as the reactant, and carbon tetrachloride as solvent (*J. Amer. Chem. Soc.*, 1936, **58**, 2101; 1938, **60**, 2835; *Chem. Reviews*, 1941, **29**, 37). He concluded that the rate is given by the expression $-d[Br_2]/dt = k[A][Br_2]^{\frac{1}{2}}[I_2]^{\frac{1}{2}}$, and by a selection of certain of Bruner's measurements decided that the bromination of benzene showed similar kinetics. Thereupon he proposed a mechanism for aromatic substitution, involving an attack by BrI_3 to give an intermediate which then reacted with IBr_2^- ions formed from $(IBr)_2$. In the evaluation of the rate-expression it was assumed that $[IBr]^2$ is proportional to $[I_2]$ and $[Br_2]$, which is permissible only if IBr is considerably dissociated; this is not the case, as IBr is dissociated only to the extent of 9% in carbon tetrachloride solution at 25° (Yost *et al.*, *J. Amer. Chem. Soc.*, 1393, **55**, 3876). Further, in this formulation bromine plays no part in the reaction other than to give iodine bromide, so that the proposed mechanism cannot explain the attainment of a maximum rate with increasing amounts of iodine, which is a characteristic feature of these reactions.

The compounds hitherto selected for the investigation of the iodine catalysis of bromination have not been especially suitable. Since the reaction with benzene is very slow, high concentrations of bromine have to be used for the measurements. Likewise phenanthrene is not a favourable compound, because bromine substitution tends to be accompanied by addition (cf. Kharasch, White, and Mayo, *J. Org. Chem.*, 1938, **2**, 574). Measurements that we have made with phenanthrene in carbon tetrachloride solution showed that it was not possible to obtain reproducible results, even in an atmosphere of dry nitrogen. Traces of oxygen appear to react with the hydrogen bromide present and initiate a bromine atom-chain addition. In chloroform solution, on the other hand, the substitution reaction is relatively favoured and more reproducible results were obtained, and it was found that with M/40-reactants the order with respect to iodine, when present at low concentrations, was $\sim 1{\cdot}5$.

Iodine-catalysed bromination is conveniently studied with a more rapidly reacting hydrocarbon such as mesitylene. Measurements have been made in carbon tetrachloride and chloroform solution, and the results found to conform with those obtained for iodine-catalysed bromine addition (Waters, Caverhill, and Robertson, *J.*, 1947, 1168), the order being dependent on the amount of added iodine.

The simplest method of determining the kinetics of these reactions is to measure the rates on

changing the concentrations of the reactants separately. This is illustrated for the bromination of mesitylene in carbon tetrachloride, at 24° :

	$[I_2]$ =	0.	M/800.		M/400.
M/40-A + M/40-Br_2, time (mins., $x = 10$)		72	14		6·5
n (IBr) corr.				*1·1*	
M/80-A + M/80-Br_2, time (mins., $x = 10$)		—	45		21
n (IBr) corr.				*1·1*	
n (A + Br_2).....			*2·7*		*2·7*

The results for the same reaction in chloroform, M/80-reactants, at 24°, are now given :

	$[I_2]$ =	0.	M/1600.		M/800.
Time (mins., $x = 25$)		48	1·80 *		0·77
n (IBr) corr.				*1·2*	

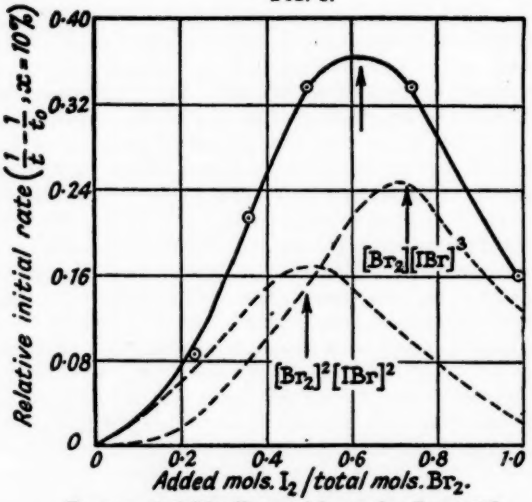
* Reactants M/40, $t = 0{\cdot}90$: n(A + Br_2) = *2·0*.

The n values for iodine bromide require a correction (small in the above reactions) (*a*) for the simultaneous uncatalysed reaction and (*b*) for the amount of bromine removed by combination with iodine. These results indicate that for low concentrations of added iodine the order with respect to iodine bromide approaches unity, *i.e.*, when the bromine is in the concentration region M/40. With higher concentrations of bromine, the order for iodine bromide becomes greater even when the amount of added iodine, relative to the bromine, is small, as is shown in the reaction of *o*-xylene with bromine : (M/2-Reactants, at 24°, in carbon tetrachloride solution.)

	$[I_2]$ =	0·008M.		0·016M.
Time (mins., $x = 20$)		78		18
n (corr.) (IBr)			*2·0*	

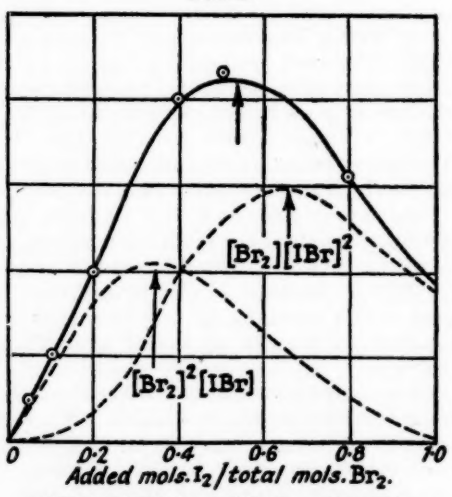
With greater amounts of iodine an approximate analysis of the experimental results can be made by a graphical method. A similar treatment can also be applied to Bruner's measure-

FIG. 1.



Benzene + 0·28M-Br_2, *with varying* I_2, *at* 25°. *Bruner's* (loc. cit.) *results.*

FIG. 2.



M/40-*Mesitylene* + M/40-Br_2, *with varying* I_2, *in* CCl_4 *at* 24°.

ments in the bromination of benzene. From his results (Table 3, *loc. cit.*) the relative initial rates, calculated as $1/t$ (since the contribution of the uncatalysed reaction is negligible) may be obtained and are plotted in Fig. 1. The iodine is present chiefly as iodine bromide, and it may be calculated from Bruner's other results (Tables 1 and 2, *loc. cit.*) that at low concentrations of iodine the rate is proportional to $[Br_2]^2[IBr]^2$. A curve representing this reaction is constructed to coincide with the experimental curve at 0·1 mol. of I_2; this is the broken curve showing a maximum at 0·50 mol. of I_2, and there is included a correction, which is small, to allow for the dissociation of the iodine bromide. The difference between this curve and the experimental curve gives a second curve which should correspond with a rate proportional to $[Br_2][IBr]^3$, as the total order of the reaction remains the same and the order for iodine bromide becomes

greater as the iodine is increased. This new curve is found to approximate to the calculated curve for this reaction, and in particular to have its maximum rate at 0·74 mol. of I_2 (calc., 0·75).

The experimental maximum is between the theoretical maxima, rather more in the direction of the $[Br_2][IBr]^2$ reaction, and correspondingly the relative contribution of this reaction is somewhat greater under these conditions, as shown by the vertical distances in the diagram. The iodine-catalysed bromination of benzene, at high concentrations of bromine, may therefore be represented by

$$-d[Br_2]/dt = k[Br_2]^2[IBr]^2 + k'[Br_2][IBr]^2$$

A similar treatment is possible for the iodine-catalysed bromination of mesitylene, M/40-reactants, in carbon tetrachloride solution (Fig. 2). A curve for the rate proportional to $[Br_2]^2[IBr]$ is drawn to coincide with the experimental curve at 0·05 mol. of I_2 [when n (IBr) was found to be unity], and has a maximum at 0·35 mol. of I_2. On subtracting this curve from the experimental curve, a second curve is obtained with maximum at 0·65 mol. of I_2. This curve has approximately the characteristics of the reaction for which the rate is $k'[A][Br_2][IBr]^2$, with a maximum at 0·66 mol of I_2. At the experimental maximum rate the contribution of the higher-order reaction (as determined by the vertical distances) is more considerable, and there is a corresponding disposition of this maximum between the maxima of the two contributing reactions. It may be concluded, therefore, that the rate-expression for the iodine-catalysed bromination of mesitylene in carbon tetrachloride, for low concentrations of bromine, is

$$-d[Br_2]/dt = k[A][Br_2]^2[IBr] + k'[A][Br_2][IBr]^2$$

Discussion.—Halogen substitution, like halogen addition, may be formulated as a two-stage process. In bromine substitution the first stage is an electrophilic attack by a bromine molecule polarised by a polar surface, or solvent dipoles, or by a second molecule of bromine, to join with RH forming an addition compound, RH,Br_2; the second stage is the anionisation of a bromine atom from this with the simultaneous separation of a hydrogen atom as hydrogen bromide. With added iodine it is suggested that iodine tribromide replaces the bromine in the first stage; its amount present must be small (cf. Morton, *Proc. Royal Soc.*, 1929, *A*, **124**, 609) and its concentration therefore proportional to $[Br_2][IBr]$. Like Br_2, it is favourably polarisable, $[Br^+][IBr_2^-]$, for electrophilic attack. In the second stage of the reaction iodine bromide operates by removal of a bromine atom from RH,Br_2 as the ion IBr_2^-. If the catalytic effect in the first stage is relatively less effective than in the second stage, *i.e.*, occurring to an appreciable extent only when the added iodine becomes considerable, then the bromination of mesitylene may be represented, (*a*) in chloroform, $[I_2]$ small, (*b*) in carbon tetrachloride, $[I_2]$ small, (*c*) in either solvent, $[I_2]$ considerable, as follows :

(*a*) $RH + Br_2 \rightleftharpoons RH,Br_2$; $RH,Br_2 + IBr \longrightarrow RBr + HIBr_2$
(*b*) $RH + Br_4 \rightleftharpoons RH,Br_2 + Br_2$; ditto
(*c*) $RH + IBr_3 \rightleftharpoons RH,Br_2 + IBr$; ditto

The explanation of the overall fifth-order reaction measured by Bruner is more doubtful. If, as seems probable, these reactions proceed by a series of bimolecular steps, in each of which one of the reactants is in excess, then the following formulation would be in accord with the observed kinetics of the two simultaneous reactions :

(i) $Br_2 + Br_2 \longrightarrow Br_4$; $Br_4 + IBr \longrightarrow IBr_5$; $IBr_5 + RH \longrightarrow RHBr_2 + IBr_3$; $RHBr_2 + IBr \longrightarrow RBr + HIBr_2$
(ii) $Br_2 + IBr \longrightarrow IBr_3$; $IBr_3 + IBr \longrightarrow I_2Br_4$; $I_2Br_4 + RH \longrightarrow RHBr_2 + 2IBr$; $RHBr_2 + IBr \longrightarrow RBr + HIBr_2$

This theory demands the existence of the compounds IBr_5 and I_2Br_4; the amounts formed must be small, even at high bromine concentrations, but such compounds may be suitably polarisable for electrophilic attack, towards the structures $[Br^+][IBr_4^-]$ and $[Br^+][I_2Br_3^-]$.

Experimental.

The following compounds were used : mesitylene, b. p. 164°/747 mm.; *o*-xylene, b. p. 143°/756 mm. The technique was as previously described, chloramine-T being used instead of iodine for the back titrations (*J.*, 1943, 276). Herewith is a typical set of measurements in detail.

M/40-Mesitylene + M/40-Br_2 + M/400-iodine, in carbon tetrachloride at 24° under nitrogen; reaction mixture 10 ml.; 1-ml. samples added to N/80-sodium arsenite and back-titrated with N/80-chloramine-T.

Time (mins.).	Titre (ml.).	Br_2, %, absorbed (x).	Time (mins.).	Titre (ml.).	Br_2, %, absorbed (x).
0	0·65	0	0	0·56	0
6	1·04	9	5·2	0·90	7·5
12	1·39	17	11·3	1·32	17
19	1·82	27	21	1·81	28

The points lay on a smooth curve from which the value, $t = 6{\cdot}5$ ($x = 10$) was taken.

The values for M/40-mesitylene + M/40-bromine and different amounts of iodine in carbon tetrachloride at 24°, for $x = 10\%$ bromine absorption (Fig. 2) are as times (minutes): no I_2, $t = 72$; M/400-I_2, $t = 6{\cdot}5$; M/200-I_2, $t = 3{\cdot}4$; M/100-I_2, $t = 1{\cdot}8$; M/80-I_2, $t = 1{\cdot}65$; M/50-I_2, $t = 2{\cdot}4$; M/25-I_2, $t = 4{\cdot}7$. Other measurements have been quoted in the text.

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201. *Carbon–Halogen Bond Energies in the Acetyl Halides.*

By A. S. CARSON and H. A. SKINNER.

From measurements of the heats of hydrolysis of the acetyl halides, the following values (in kcals.) were obtained for the heats of formation (Q_f): $Q_f(CH_3{\cdot}COF, liq.) = 110{\cdot}6$; $Q_f(CH_3{\cdot}COCl, liq.) = 65{\cdot}8$; $Q_f(CH_3{\cdot}COBr, liq.) = 53{\cdot}9$; $Q_f(CH_3{\cdot}COI, liq.) = 39{\cdot}7$. These Q_f values, taken in conjunction with a probable value, $Q_f(CH_3{\cdot}CO) = 11{\cdot}3$ kcals., for the heat of formation of the acetyl radical, give 110, 76·7, 62·0, and 46·0 kcals., respectively, for the C–F, C–Cl, C–Br, and C–I bond dissociation energies in the acetyl halides.

THE dissociation energy of the carbon–halogen bond in the molecule $CH_3{\cdot}COX$ may be expressed by the equation

$$D(CH_3{\cdot}CO - X) = Q_f(CH_3{\cdot}COX) - Q_f(CH_3{\cdot}CO) - Q_f(X) \quad . \quad . \quad . \quad . \quad (1)$$

where the terms in Q_f are heats of formation from *elements* in their standard states. Accordingly, if $Q_f(CH_3{\cdot}CO)$ is known, a knowledge of the heats of formation of the acetyl halides is then sufficient to provide the bond dissociation energies of the C–halogen bonds in these compounds.

Berthelot and Longuinine (*Ann. Chim. Phys.*, 1875, **6**, 289) measured the heats of hydrolysis of acetyl chloride, bromide, and iodide, *viz.*,

$$CH_3{\cdot}COX(liq.) + H_2O(aq.) \longrightarrow CH_3{\cdot}CO_2H\ (aq.) + HX(aq.) + Q \quad . \quad . \quad . \quad . \quad (2)$$

from which the value $Q_f(CH_3{\cdot}COX, liq.)$ may be derived as

$$Q_f(CH_3{\cdot}COX, liq.) = Q_f(CH_3{\cdot}CO_2H, aq.) + Q_f(HX, aq.) - Q_f(H_2O, liq.) - Q \quad . \quad . \quad (3)$$

No previous measurement of the heat of hydrolysis of acetyl fluoride appears to have been made.

We have described elsewhere (Carson, Hartley, and Skinner, *Proc. Roy. Soc.*, 1949, *A*, 195, 500) an adiabatic calorimeter suitable for the measurement of heats of hydrolysis, which we have now used in a reinvestigation of the heats of hydrolysis of acetyl chloride, bromide, and iodide, and also of acetyl fluoride. The new measurements agree reasonably closely with those of Berthelot and Longuinine.

EXPERIMENTAL.

(a) *Preparation of Compounds.*—Acetyl chloride was a B.D.H. "AnalaR" product, carefully fractionated in a Fenske packed column; b. p. 51·2°/769 mm. The product was finally distilled over roasted lime in a vacuum, and collected in weighed glass phials. Analysis of the chlorine content of chosen samples (weighed as AgCl) showed 99·8—100% purity.

Acetyl bromide was also an "AnalaR" product, and was subjected to a careful fractionation in a Fenske column; b. p. 75·5°/758 mm. The product was finally distilled from bulb to bulb in a vacuum, and sealed in weighed glass phials. Analysis of the bromine content (weighed as AgBr) of selected samples showed 99·8—100% purity.

Acetyl iodide was prepared by reaction between the chloride and hydriodic acid (Staudinger, *Ber.*, 1913, **46**, 1417). The crude product was fractionated in the Fenske column, and the almost colourless distillate, b. p. 105·5°, shaken with a little mercury to remove traces of free iodine, and later fractionated in a vacuum. The product was finally obtained as a clear colourless liquid. Analysis of the iodine content (weighed as AgI) of selected samples showed an average purity of 99·5%.

Acetyl fluoride was prepared by reaction of potassium fluoride dissolved in glacial acetic acid with acetyl chloride (Nesmejanov and Kahn, *Ber.*, 1934, **67**, 370). The crude product was fractionated in a vacuum, the first and the last fraction being discarded. The product thus obtained was not pure, containing 10% or more of unchanged acetyl chloride. In determining the heat of hydrolysis of acetyl fluoride, we have made correction for the chlorine impurity as determined by analysis.

(b) *Heats of Hydrolysis.*—(i) *Acetyl chloride.* The heats of hydrolysis were obtained by measuring the heat generated on breaking glass phials containing a known weight of acetyl chloride into a known weight of distilled water, contained within the reaction vessel of the calorimeter. Reactions were carried out at atmospheric pressure. The results of six experiments with acetyl chloride are set out in the table. The values of Q_f(HCl, aq.) are taken from Rossini's "Tables of Selected Values of Thermodynamic Constants." $Q_f(CH_3{\cdot}CO_2H, aq.)$ values used in deriving $Q_f(CH_3{\cdot}COCl, liq.)$ were based on $Q\ (CH_3{\cdot}CO_2H, liq.) = 116{\cdot}4$ kcals. (Rossini, private communication) and the heats of dilution of liquid acetic acid (Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold, 1936).

Heat of hydrolysis of acetyl chloride.

Expt.	Reaction.	AcCl (g.).	ΔT (obs.).	W.E. (cals./°c.).	$-\Delta H$ (kcals.).	Q_f(AcCl, liq.) (kcals.).
1	AcCl + $66H_2O$	4·625	1·014°	1277	22·0	65·77
2	AcCl + $87H_2O$	5·029	1·088	1308	22·21	65·68
3	AcCl + $74H_2O$	4·708	1·024	1287	21·98	65·84
4	AcCl + $94H_2O$	6·957	1·440	1359	22·09	65·83
5	AcCl + $90H_2O$	6·051	1·280	1333	22·14	65·76
6	AcCl + $85H_2O$	5·622	1·202	1318	22·12	65·77

Mean $Q_f(CH_3{\cdot}COCl, liq.) = 65{\cdot}78$ kcals. mole^{-1}. Maximum deviation from mean = ± 0·10 kcal. Standard deviation of mean = ± 0·022 kcal. $\lambda_{vap.}$ (AcCl) = 6·84 kcals. (Landolt–Börnstein). Q_f(AcCl, gas) = 58·94 kcals. mole^{-1}.

(2) *Acetyl bromide.* Results of six experiments using acetyl bromide are set out in the appropriate table. Values of Q_f(HBr, aq.) were taken from Rossini (*op. cit.*).

Heat of hydrolysis of acetyl bromide.

Expt.	Reaction.	AcBr (g.).	ΔT (obs.).	W.E. (cals./°c.).	$-\Delta H$ (kcals.).	Q_f(AcBr, liq.) (kcals.).
1	AcBr + $98H_2O$	5·598	0·807°	1288	22·83	54·07
2	AcBr + $140H_2O$	7·362	1·023	1359	23·21	53·77
3	AcBr + $128H_2O$	7·916	1·080	1359	22·79	54·17
4	AcBr + $101H_2O$	10·183	1·407	1361	23·07	53·83
5	AcBr + $125H_2O$	8·194	1·130	1359	23·04	53·91
6	AcBr + $120H_2O$	8·518	1·185	1359	23·25	53·70

Mean Q_f(AcBr, liq.) = 53·9 kcals. mole^{-1}. Maximum deviation from mean = ±0·27 kcal. Standard deviation of mean = ±0·067 kcal. $\lambda_{vap.}$ (AcBr) = 7·3 kcals. (Landolt–Börnstein). Q_f(AcBr, gas) = 46·6 kcals.

(3) *Acetyl iodide.* The results of five experiments using acetyl iodide are set out in the table. The values of Q_f(HI, aq.) were taken from Rossini (*op. cit.*). The final value for $Q_f(CH_3{\cdot}COI, liq.)$ is a slightly adjusted figure to compensate for the impurity (*ca.* ½%) present in the samples of acetyl iodide.

Heat of hydrolysis of acetyl iodide.

Expt.	Reaction.	AcI (g.).	ΔT (obs.).	W.E. (cals./° c.).	$-\Delta H$ (kcals.).	Q_f (AcI) (kcals.).
1	AcI + $140H_2O$	8·458	0·804°	1334	21·56	39·98
2	AcI + $143H_2O$	7·915	0·752	1329	21·45	40·09
3	AcI + $136H_2O$	9·016	0·859	1339	21·68	39·87
4	AcI + $121H_2O$	11·616	1·087	1360	21·64	39·88
5	AcI + $136H_2O$	8·760	0·836	1335	21·63	39·92

Mean $Q_f(CH_3{\cdot}COI, liq.) = 39{\cdot}95$ kcals. (obs.) = 39·75 kcals. (corr.). Maximum deviation from mean = ±0·14 kcal. Standard deviation of mean = ±0·036 kcal. $\lambda_{vap.}$ ($CH_3{\cdot}COI$) ≈ 7·9 kcals. (assumed). $Q_f(CH_3{\cdot}COI, gas) = 31{\cdot}8$ kcals. mole^{-1}.

(4) *Acetyl fluoride.* The heat of hydrolysis of acetyl fluoride was obtained by measuring the heat of reaction with aqueous sodium hydroxide;

$$CH_3{\cdot}COF(liq.) + 2NaOH(aq.) \longrightarrow NaF(aq.) + CH_3{\cdot}CO_2Na(aq.) + H_2O(liq.) \quad . \quad . \quad (4)$$

In this way, hydrogen fluoride formed by the aqueous hydrolysis is removed by the alkali, and spurious heat effects that would otherwise arise from its attack on the glass phial are avoided. The hydrolysis with alkali is a rapid reaction relative to the aqueous hydrolysis, which gives an additional reason for choosing this reaction. The products of reaction were analysed for chlorine content at the end of each measurement, to allow corrections to be made for the acetyl chloride impurity present in the fluoride samples. The results as presented in the table below are the corrected values.

Heat of hydrolysis of acetyl fluoride.

Expt.	Reaction.	AcF (g.).	ΔT (obs.).	W.E. (cals./° c.).	$-\Delta H$ (kcals.).	Q_f(AcF) (kcals.).
1	AcF + 2NaOH(67)	1·69	0·905°	1307	43·4	110·0
2	AcF + 2NaOH(50)	1·97	1·033	,,	42·5	110·8
3	AcF + 2NaOH(50)	2·35	1·221	,,	42·1	111·2
4	AcF + 2NaOH(70)	1·506	0·783	,,	43·1	110·4

Mean Q_f (AcF, liq.) = 110·6 kcals. Maximum deviation from mean = ±0·6 kcal. $\lambda_{vap.}$ (AcF) ≈ 6 kcals. (assumed). Q_f (AcF, gas) = 104·6 kcals.

The determination of $Q_f(CH_3{\cdot}COF, liq.)$ from the heat of reaction (4) requires a knowledge of the heats of formation of aqueous NaOH, $CH_3{\cdot}CO_2Na$, and NaF; Q_f(NaOH, aq.) and Q_f(NaF, aq.) values were taken from the compilation by Bichowsky and Rossini (*op. cit.*), and the values for sodium acetate from the data of Richards and Mair (*J. Amer. Chem. Soc.*, 1929, **51**, 737) in conjunction with the value here assumed for $Q_f(CH_3{\cdot}CO_2H, liq.)$ of 116·4 kcals.

In view of the corrections made to allow for the impurity in the acetyl fluoride samples, we make no claim for high accuracy in our figures for $-\Delta H$ and Q_f(AcF, liq.) as given here. We hope to re-investigate the heat of hydrolysis of acetyl fluoride later with pure samples of substance.

Discussion.

The Value of $Q_f(CH_3{\cdot}CO)$.—Several investigators (Gorin, *J. Chem. Physics*, 1939, **7**, 256, $E \geqslant 17$; Benson and Forbes, *J. Amer. Chem. Soc.*, 1943, **65**, 1399, $E = 16 \pm 2$; Herr and Noyes, *ibid.*, 1940, **62**, 2052, $E \approx 18$; Blacet and Blaedel, *ibid.*, p. 3374 *) have given estimates of the activation energy (E) associated with the decomposition of the acetyl radical,

$$CH_3{\cdot}CO \longrightarrow CH_3 + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

There seems little doubt that the value of E is at least as high as 10 kcals., and the majority of estimates place it from 10 to 20 kcals. A fairly full discussion on the experimental data and E values has been given by Steacie (" Atomic and Free Radical Reactions," Reinhold, 1946), who recommends $E \approx 17$ kcals. as the most probable value.

It is reasonable to expect that the activation energy, E, and the dissociation energy $D(CH_3 - CO)$ are closely similar, if not identical; in this event we may write

$$D(CH_3 - CO) \approx E = Q_f(CH_3{\cdot}CO) - Q_f(CH_3) - Q_f(CO) \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The values $Q_f(CO) = 26{\cdot}41$ kcals. and $Q_f(CH_3) = -32{\cdot}1$ kcals. are both reasonably well established, so that (7) reduces to

$$Q_f(CH_3{\cdot}CO) = E - 5{\cdot}7 \text{ kcals.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

If we accept Steacie's recommended value (*op. cit.*) for E (*viz.*, $\approx$17 kcals.), the value $Q_f(CH_3{\cdot}CO) = 11{\cdot}3$ kcals. is obtained. Although this value for $Q_f(CH_3{\cdot}CO)$ cannot claim to be well established, there is much subsidiary evidence that it is a correct assessment within limits of ± 5 kcals. (see later).

The Values $Q_f(X)$.—The quantities $Q_f(X)$, where X = Cl, Br, and I, are now known to a high degree of precision; the figures quoted here are those recommended by Rossini (*op. cit.*), *viz.*, $Q_f(Cl) = 29{\cdot}0$, $Q_f(Br) = 26{\cdot}7$, $Q_f(I) = 25{\cdot}5$ kcals. In the case of $Q_f(F)$, it appears to be necessary to discard the value of -32 kcals. which has hitherto been generally accepted. Some reason to doubt the old value [which corresponds to the value $D(F{-}F) = 64$ kcals.] first appeared from the determination of $D(Cl{-}F)$ by Wahrhaftig (*J. Chem. Physics*, 1942, **10**, 248). The recent measurement of the heat of formation of ClF by Schmitz and Schumacher (*Z. Naturforsch.*, 1947, **2**, 362) [$Q_f(ClF, g.) = 15 \pm \frac{1}{2}$ kcals.], coupled with the determination of $D(Cl{-}F)$ at $60{\cdot}3 \pm 0{\cdot}5$ kcals. (or possibly, $58{\cdot}9 \pm 0{\cdot}5$) by the same authors (*ibid.*, p. 359) seems definitely to prove that $D(F{-}F)$ is not greater than 33·4 kcals. Accordingly, we have chosen $Q_f(F)$ at $-16{\cdot}7$ kcals., as the most probable value.

Dissociation Energies of Acetyl–Halogen Bonds.—The bond dissociation energies $D(CH_3{\cdot}CO{-}X)$ as given by eqn. (1), using the listed values of $Q_f(X)$, $Q_f(CH_3{\cdot}CO)$, and $Q_f(CH_3{\cdot}COX, gas)$, are collected below.

Values of $D(CH_3{\cdot}CO{-}X)$, *kcals.*

Compound.	$D(CH_3{\cdot}CO{-}X)$.	Compound.	$D(CH_3{\cdot}CO{-}X)$.
$CH_3{\cdot}COF$	110·0	$CH_3{\cdot}COBr$	62·0
$CH_3{\cdot}COCl$	76·7	$CH_3{\cdot}COI$	46·0

The value $D(CH_3{\cdot}CO{-}I) = 46$ kcals. may be compared with the figure 50·7 kcals. obtained by Butler and Polanyi (*Trans. Faraday Soc.*, 1943, **39**, 19) from studies of the kinetics of thermal decomposition of acetyl iodide, and with an earlier estimate of 43·1 kcals. by Jones (*J. Amer. Chem. Soc.*, 1939, **61**, 3284) from similar studies. Neither of these kinetic studies claims high accuracy for the estimated C–I dissociation energy. Butler and Polanyi's value for $D(CH_3{\cdot}CO{-}I)$ corresponds to $Q_f(CH_3{\cdot}CO) = 6{\cdot}6$ kcals., and lies within the limits of error (± 5 kcals.) which we have attached to the probable value of $Q_f(CH_3{\cdot}CO)$. We may note that the value $Q_f(CH_3{\cdot}CO) = 11{\cdot}3$ kcals. corresponds to $D(CH_3{\cdot}CO{-}H) = 80{\cdot}2$ kcals., and to $D(CH_3{\cdot}CO{-}CH_3) = 72{\cdot}6$ kcals.; the former fits in well with the value $D(H{-}CHO) = 78$ kcals. estimated (as an upper limit) by Gorin (*loc. cit.*) from photo-dissociation studies, and the latter agrees closely with $D(CH_3{-}CHO) = 75(\pm 2)$ kcals., obtained by Graham and Rollefson (*J. Chem. Physics*, 1940, **8**, 98).

* These authors consid er the disappearance of $CH_3{\cdot}CO$ radicals results from a bimolecular reaction, $CH_3{\cdot}CO + M \longrightarrow CH_3 + CO + M$, to which an activation energy of 9·6 kcals. is ascribed.

The fact that $D(CH_3{\cdot}CO{-}I)$ is considerably less than $D(CH_3{-}I)$ is at first sight puzzling—as Butler and Polanyi pointed out—since one would expect the C–I bond in $CH_3{\cdot}COI$ to possess double-bond character, arising from the resonance contribution of the structure $CH_3{\cdot}C{<}^{O^-}_{I^+}$. The difficulty disappears when one appreciates that $D(CH_3{\cdot}CO{-}H)$ is markedly weaker than $D(CH_3{-}H)$, indicative of a large hyperconjugation energy in the acetyl radical. Roberts and Skinner (in course of publication) have discussed this point in more detail elsewhere.

The value for $D(CH_3{\cdot}CO{-}F)$ enables us to make a plausible estimate of the unknown dissociation energy $D(CH_3{-}F)$. The bond dissociation energy differences (*idem, ibid.*), $D(CH_3{-}X)$ minus $D(CH_3{\cdot}CO{-}X)$, vary with change in X as follows:

X =	H.	CH_3.	I.	Br.	Cl.	–OH.
Diff.	21·8	11·8	9·0	5·4	4·0	−6·0

i.e., decreasing in magnitude as the electronegativity of X increases. One might expect the difference in case of the highly electronegative fluorine atom to be of similar magnitude to that shown when X = OH. This would lead to a value of *ca.* 105 kcals. for $D(CH_3{-}F)$. A similar value is reached by a different approach; thus, if one calculates the *mean* bond-energy term values E(C–H) in CH_4, and E(C–Cl) in CCl_4, assuming L = 171·7 kcals. for the latent heat of sublimation of carbon, the E values are found to be slightly less (2—3 kcals.) than the quantities $D(CH_3{-}H)$ and $D(CH_3{-}Cl)$. For carbon tetrafluoride, the E(C–F) value is 100·2 kcals.: so that one might expect $D(CH_3{-}F)$ to be rather larger than 100 kcals.

THE UNIVERSITY, MANCHESTER. [*Received, September* 18*th*, 1948.]

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202. *The Reaction of* N-*Bromosuccinimide with Methyl Oleate and Other Vegetable-oil Derivatives.*

By DONALD A. SUTTON and J. DUTTA.

N-Bromosuccinimide reacts with methyl oleate to give an oil which can be molecularly distilled without decomposition, and contains an appreciable proportion of the dibromo-substitution product. The oil reacts with chromatographic alumina; allyl bromide itself does not similarly react but 3-bromo*cyclo*hexene undergoes a vigorous decomposition. The bromo-substitution products from linoleic ester, linolenic ester, and linseed oil are unstable; they cannot be molecularly distilled without decomposition. The work has a bearing on a current hypothesis which states that the reaction between olefins and *N*-bromosuccinimide is a free-radical reaction.

THE reaction between *N*-bromosuccinimide and methyl oleate was first investigated by Ziegler and his co-workers (*Annalen*, 1942, **551**, 80), who reported that the product obtained from equimolecular proportions of the reactants was an oil (assumed to be a monobromo-derivative) which could not be distilled or smoothly transformed by dehydrobromination into the diene ester. It was found that products containing larger amounts of combined bromine could readily be made when greater proportions of *N*-bromosuccinimide were employed. Teeter (*J. Amer. Oil Chem. Soc.*, 1948, **25**, No. 7, 243) treated *N*-bromosuccinimide with methyl linoleate and with the mixed methyl esters of soya-bean oil fatty acids; * he found that the brominated esters were somewhat unstable and recommended that the preparation should be carried out at a fairly low temperature (70°). Teeter also investigated the reaction of the brominated esters with sodium methoxide and with sodium and cuprous cyanides.

The present work on the reaction between methyl oleate and *N*-bromosuccinimide was undertaken because the expected monobromo-derivatives (I) and (II), or a mixture of both, was required for a synthesis in connection with a research into the thermal polymerisation of drying oils.

$CH_3{\cdot}[CH_2]_6{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}[CH_2]_6{\cdot}CO_2Me$
Methyl oleate.

→ $CH_3{\cdot}[CH_2]_6{\cdot}CHBr{\cdot}CH{:}CH{\cdot}CH_2{\cdot}[CH_2]_6{\cdot}CO_2Me$
Methyl 10-bromoheptadec-8-enecarboxylate
(11-bromo-Δ^9-oleate).
(I.)

→ $CH_3{\cdot}[CH_2]_6{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CHBr{\cdot}[CH_2]_6{\cdot}CO_2Me$
Methyl 7-bromoheptadec-8-enecarboxylate
(8-bromo-Δ^8-oleate).
(II.)

* The chief components of this mixture are linoleic acid (*ca.* 50%) and oleic acid (*ca.* 30%).

The course of the substitutive bromination has, in addition, a considerable theoretical interest, for Waters (*Nature*, 1944, **154**, 772; *J.*, 1946, 409) considers that *N*-bromosuccinimide reacts with olefins after the homolytic fission of a covalent carbon–hydrogen bond:

$$\cdot CH_2 \cdot CH{:}CH \cdot \longrightarrow \cdot \dot{C}H \cdot CH{:}CH \cdot \xrightarrow{N\text{-Bromosuccinimide}} \cdot CHBr \cdot CH{:}CH \cdot$$

so that the reaction is essentially of the free-radical type. If this is the mechanism of reaction, then the number of possible monobromo-isomerides from methyl oleate is four, since the intermediate free-radical forms could isomerise as in autoxidation processes (compare Farmer, Koch, and Sutton, *J.*, 1943, 541; Bolland and Gee, *Trans. Faraday Soc.*, 1946, **42**, 236) and lead to the formation of (III) and (IV) in addition to (I) and (II).

$CH_3 \cdot [CH_2]_6 \cdot \dot{C}H \cdot CH{:}CH \cdot CH_2 \cdot [CH_2]_6 \cdot CO_2Me$

$\rightleftharpoons$

$CH_3 \cdot [CH_2]_6 \cdot CH{:}CH \cdot \dot{C}H \cdot CH_2 \cdot [CH_2]_6 \cdot CO_2Me$

$\downarrow$

$CH_3 \cdot [CH_2]_6 \cdot CH{:}CH \cdot CHBr \cdot CH_2 \cdot [CH_2]_6 \cdot CO_2Me$

Methyl 8-bromoheptadec-9-enecarboxylate (9-bromo-Δ^{10}-oleate).

(III).

$CH_3 \cdot [CH_2]_6 \cdot CH_2 \cdot CH{:}CH \cdot \dot{C}H \cdot [CH_2]_6 \cdot CO_2Me$

$\rightleftharpoons$

$CH_3 \cdot [CH_2]_6 \cdot CH_2 \cdot \dot{C}H \cdot CH{:}CH \cdot [CH_2]_6 \cdot CO_2Me$

$\downarrow$

$CH_3 \cdot [CH_2]_6 \cdot CH_2 \cdot CHBr \cdot CH{:}CH \cdot [CH_2]_6 \cdot CO_2Me$

Methyl 9-bromoheptadec-7-enecarboxylate (10-bromo-Δ^8-oleate).

(IV.)

In the case of methylene-interrupted unsaturation, such as occurs in linoleic and linolenic esters, isomerisation of the intermediate free-radical forms would lead to formation of brominated compounds containing a system of conjugated double bonds. Thus linoleic ester could give rise to (V) and (VI) as a result of double-bond movement in the free radical:

$CH_3 \cdot [CH_2]_4 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2Et$

Ethyl linoleate.

$\rightarrow$ $CH_3 \cdot [CH_2]_4 \cdot CHBr \cdot CH{:}CH \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2Et$

Ethyl 12-bromoheptadeca-8 : 10-dienecarboxylate (13-bromo-$\Delta^{9:11}$-linoleate).

(V.)

$\rightarrow$ $CH_3 \cdot [CH_2]_4 \cdot CH{:}CH \cdot CH{:}CH \cdot CHBr \cdot [CH_2]_7 \cdot CO_2Et$

Ethyl 8-bromoheptadeca-9 : 11-dienecarboxylate (9-bromo-$\Delta^{10:12}$-linoleate).

(VI.)

Double-bond movement of the kind visualised above has not been recorded in the great majority of the cases of reaction between olefins and *N*-bromosuccinimide investigated since 1942 (Djerassi, *Chem. Reviews*, 1948, **43**, 271). In the present work it was found that the products obtained when *N*-bromosuccinimide reacted with linoleic ester, linolenic ester, and linseed oil contained conjugated unsaturation, but the amounts of conjugated compounds present (estimated by ultra-violet spectroscopy) were not large. The triene conjugation observed in the case of bromo-linoleic ester prepared in boiling carbon tetrachloride was not present in large amount; bromo-linoleic ester prepared under mild conditions (similar to Teeter's) contained no triene conjugation and no band near 232 mμ characteristic of diene conjugation but developed some triene conjugation when heated at 100°. The above data can be accounted for by the hypothesis that the bromo-ester readily undergoes an allylic rearrangement similar to that recorded by Karrer and Ringli in the case of brominated diallyl (*Helv. Chim. Acta*, 1947, **30**, 863, 1771), followed by partial dehydrobromination. These facts do not lend support to Waters's views.

In a typical experiment, methyl oleate reacted with an equimolecular proportion of *N*-bromosuccinimide in boiling carbon tetrachloride for 4½ hours to give an oil containing some two-thirds of the theoretical amount of combined bromine. The oil was comparatively stable; no hydrogen bromide was evolved during its preparation or subsequent molecular distillation at 78°. Although the overall percentage of combined bromine was less than that required for the pure monobromo-derivative, the product contained an appreciable proportion of the dibromo-compound as was shown by fractionation in a falling-film molecular still (Farmer and Sutton, *J. Soc. Chem. Ind.*, 1946, **65**, 164). By molecular distillation at 78° the oil was divided into a distillate (*ca.* 80%) and a residue (*ca.* 20%); the bromine content of the latter (28·7%) corresponded to a mixture containing some 53% of the dibromo-compound (presumably 7 : 10-dibromoheptadec-8-enecarboxylic ester) and 47% of the monobromo-compound. The

distillate probably also contained some dibromo-ester, since the fractionating efficiency of falling-film stills is poor, and, in a distillation at 86° of another batch of the bromo-ester, a distillate with a bromine content (23·9%) higher than that required for the monobromo-compound (21·3%) was obtained. It was found that the succinimide had not been completely removed from the total reaction product by filtration from carbon tetrachloride solution, since some of it distilled under the conditions used. A specimen of the molecularly distilled oil was oxidised with permanganate in acetone and yielded a mixture from which suberic, azelaic, and octoic acids were isolated and identified. Some part of the azelaic acid would result from oxidation of the methyl oleate remaining in the oil; the formation of suberic and octoic acids is consistent with the presence of both monobromo-esters (I) and (II) which would also yield some azelaic and nonoic acids:

$$\text{(I)} \xrightarrow{KMnO_4} CH_3\cdot[CH_2]_6\cdot CO_2H + CO_2H\cdot[CH_2]_7\cdot CO_2Me$$

$$\text{(II)} \xrightarrow{KMnO_4} CH_3\cdot[CH_2]_7\cdot CO_2H + CO_2H\cdot[CH_2]_6\cdot CO_2Me$$

The above oxidative scission products could also arise from monobromo-esters (III) and (IV) if these were present.

Attempts to separate the individual monobromo-esters (I) and (II) in a pure state from the molecularly distilled oil by chromatography on activated alumina were unsuccessful because the adsorbent reacted with the brominated ester and removed most of the combined bromine. Two products of the chromatographic experiments were isolated; they were apparently hydroxy-oleic esters, but the positions of the hydroxyl groups were not determined. Examination of one product by infra-red spectroscopy showed that it gave a band at a wavelength of 2·9 μ characteristic of a hydroxyl group and similar in intensity to the corresponding band given by methyl ricinoleate. The other product was hydrogenated, and the saturated ester formed was converted into the corresponding acid; examination of the latter in a Langmuir trough showed that it gave a monolayer film of the gaseous type very similar to that given by a pure specimen of 12-hydroxystearic (11-hydroxyheptadecanecarboxylic) acid in our laboratories and also similar to that of 3(?)-hydroxystearic acid (Fosbinder and Rideal, *Proc. Roy. Soc.*, **1933, 143**, *A*, 61).

It is possible that the hydroxy-oleic ester is formed as a result of reaction between the bromo-ester and aluminium hydroxide present in the chromatographic alumina. Allyl bromide itself does not react with activated alumina at room temperature, but 3-bromo*cyclo*hexene undergoes a vigorous reaction.

Linoleic and linolenic esters were also brought into reaction with *N*-bromosuccinimide in boiling carbon tetrachloride solution. In agreement with Teeter (*loc. cit.*), it was noted that fumes of hydrogen bromide were evolved during the reaction; molecular distillation of the products could not be achieved owing to their instability. As has been stated above, these brominated esters contained some conjugated unsaturation; *e.g.*, brominated linoleic ester having 13·6% of combined bromine contained 10% of conjugated triene compounds (assuming that the pure conjugated triene would give $\varepsilon = 47{,}000$ at $\lambda_{max.} = 270$ mμ). Brominated linoleic ester prepared under milder conditions had an absorption band of moderate intensity at 258 mμ which is not characteristic of acyclic diene or triene conjugation; this product developed 11% of triene conjugation after an hour's heating at 100°.

Linseed oil similarly gave off fumes of hydrogen bromide when it reacted with *N*-bromosuccinimide. The product was an oil which had film-forming properties. By saponification and concomitant dehydrobromination, the oil yielded a mixture of fatty acids which was appreciably more unsaturated than the original linseed oil and contained considerable amounts of conjugated polyenes.

Experimental.

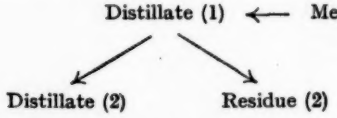
Units used.—Iodine value (I.V.) = g. of iodine per 100 g. of substance based on the amount of iodine chloride taken up by the substance in one hour by the Wijs method.

Acid value (A.V.) = mg. of potassium hydroxide equivalent to 1 g. of substance.

Bromination of Methyl Oleate.—Methyl oleate (30 g., 0·11 mole; I. V. 89), prepared from olive oil by Hilditch's method ("The Chemical Constitution of Natural Fats," 2nd edn., Chapman and Hall, London, 1947, p. 398), was dissolved in redistilled "AnalaR" carbon tetrachloride (150 c.c.), and *N*-bromosuccinimide (23 g. containing 0·10 atom of reactive bromine) was added. The whole was heated under reflux on a water-bath for 4½ hours in a slow stream of pure nitrogen with frequent shaking; there was apparently no evolution of hydrogen bromide. The solution was then cooled and filtered from succinimide at the water-pump; solvent was removed from the filtrate by distillation and finally

in a vacuum to leave an orange-red liquid (30 g.) as residue; $n_D^{25°}$ 1·4670, $d_4^{25°}$ 0·9986 (Found: Br, 14·65; I.V., 68·0. Calc. for $C_{19}H_{35}O_2Br$: Br, 21·3%; I.V., 67·7).

Distillation of the Methyl Bromo-oleate.—The product (30 g.) was subdivided by distillation in a falling-film molecular still (Farmer and Sutton, *loc. cit.*) at 78° according to the following scheme:



The fractions had the following properties:

Fraction.	Weight, g.	Br, %.	Other properties.
Original methyl bromo-oleate	30	14·65	As given above
Residue (1)	4·5	28·7	—
Distillate (1)	20	—	—
Residue (2)	11	15·0	I.V. 69·6; $n_D^{25°}$ 1·4673; $d_4^{25°}$ 0·9888
Distillate (2)	6·3	5·05	—

During the first distillation of the total methyl bromo-oleate some succinimide distilled and adhered to the wall of the still. The bromine content of residue (1) indicated the presence of dibromo-oleic ester (see p. 940), whereas residue (2) and distillate (2) contained unbrominated methyl oleate.

A second batch of methyl bromo-oleate was divided into a distillate (55 g. Found: Br, 12·0%) and a residue by molecular distillation at 78°; the residue was again subdivided at 86° into a second distillate (10 g. Found: Br, 23·9%) and a final residue (24 g.). The bromine content of the second distillate indicated the presence of distilled dibromo-ester.

Permanganate Oxidation of Distilled Methyl Bromo-oleate.—A portion of residue (2) (8·5 g.) was dissolved in acetone (90 c.c.), and the solution heated under reflux on a water-bath for 4 hours, during which potassium permanganate (50 g.) was added in small portions. The acetone was removed by distillation and finally in a vacuum to leave a solid residue which was decolorised by addition of sodium metabisulphite solution. To the decolorised solution was added sufficient aqueous sulphuric acid to render it acid to Congo-red; the organic acids present were then extracted by ether, and the aqueous layer was retained (*A*, see below). The ethereal extract was washed several times with aqueous potassium carbonate; the alkaline washings were combined, acidified, and ether-extracted. The final ethereal solution was thoroughly washed with water to remove mineral acid, and it was then dried and evaporated to yield a mixture of acids (4·1 g.) (Found: A.V., 341) which was fractionated by distillation under 2 mm. pressure through a short column to yield the folowing fractions, the residue being discarded:

Fraction.	Weight, g.	B. p.	A.V.	Fraction.	Weight, g.	B. p.	A.V.
(i)	0·4	95—100°	463	(iii)	0·6	110—135°	378
(ii)	0·3	100—110	409	(iv)	1·2	135—170	321

Fraction (iv) was a mixture containing the half-esters of suberic and azelaic acids, which were obtained and identified thus: Some of fraction (iv) (0·9 g.) was saponified by refluxing with a 10% solution of potassium hydroxide in ethyl alcohol (50 c.c.) for 2 hours; the bulk of the alcohol was removed by distillation, and the remaining solution was poured into water, acidified with dilute sulphuric acid, and thoroughly extracted with ether. The extract was washed, dried, and evaporated to yield a solid mixture of acids which was recrystallised from chloroform to give m. p. 134—138° and then from ethyl acetate to give suberic acid of m. p. 140—142° (mixed m. p. 141—143° in admixture with an authentic specimen, m. p. 143°). On evaporation of the filtrate from the chloroform recrystallisation, a solid was obtained which was recrystallised from ethyl acetate to give azelaic acid, m. p. 97—100° (mixed m. p. 99—101° in admixture with an authentic specimen, m. p. 104°).

Fraction (ii) contained *n*-octoic acid; it was converted into its *p*-bromophenacyl ester (Moses and Reid, *J. Amer. Chem. Soc.*, 1932, **54**, 2101), which, recrystallised from dilute alcohol, had m. p. 61—62° (Found: C, 56·3; H, 6·3. Calc. for $C_{16}H_{21}O_3Br$: C, 56·3; H, 6·2%) (mixed m. p. 62—64° in admixture with an authentic specimen, m. p. 65°).

Fraction (i) probably contained succinic acid (from its high acid value and positive fluorescent test after fusion with resorcinol); this acid presumably came from traces of succinimide still remaining in the distilled bromo-ester. Succinic acid was isolated from the aqueous liquor (*A*, above) thus: the liquor was continuously extracted with ether in a liquid–liquid extractor, and the extract was evaporated to yield succinic acid, m. p. 182—183° (Found: C, 41·3; H, 5·3; A.V., 930. Calc. for $C_4H_6O_4$: C, 40·6; H, 5·1%; A.V., 950) (mixed m. p. 183—185° in admixture with an authentic specimen, m. p. 185°), which gave a strongly fluorescent solution after fusion with resorcinol.

Attempted Chromatography of Methyl Bromo-oleate on Activated Alumina.—A sample of undistilled brominated methyl oleate (12 g.) (Found: Br, 18·3%) was dissolved in redistilled "AnalaR" light petroleum (100 c.c.; b. p. 40—60°) and passed through a column (12½" × 1¼") of activated alumina (Savory and Moore's "Mayfair A" brand, standardised according to Brockmann). Two yellow-brown bands appeared, and the column was developed and eluted by washing with a 2% solution of ethyl alcohol in light petroleum. Three separate portions of filtrate were collected: (*a*) the portion below the lower band, (*b*) the lower band, and (*c*) the upper band. Portion (*a*) gave 2·8 g. of an oil (Found: C, 77·2; H, 12·3; Br, 0·6%); (*b*) gave 1·9 g. of an oil, and (*c*) gave 2·3 g. of an oil. The whole of (*b*)

and (*c*) was chromatographed on more alumina in two separate columns (11″ × ¾″) and each split into two more bands, thus:

(*b*) → (*b*, i) Upper band (0·6 g. Found: Br, 0·96%)
(*b*) → (*b*, ii) Lower band (0·8 g. Found: Br, 4·3%)
(*c*) → (*c*, i) Upper band (1·8 g. Found: Br, 0·6%)
(*c*) → (*c*, ii) Lower band (0·2 g. Found: Br, 1·47%)

Some of (*c*, i) (1·0 g.) was again treated on a column of alumina (8½″ × ¾″) but was not further resolved.

Examination of two of the chromatographic products. The portion (*b*, i) was examined in a Perkin–Elmer infra-red spectrometer; it gave a band at a wave-length of 2·9μ characteristic of the hydroxyl grouping and of similar intensity to that found in methyl ricinoleate.

A sample (0·544 g.) of the final product from (*c*, i) was dissolved in methyl alcohol and hydrogenated in the presence of Adams's catalyst (0·544 g. absorbed 40 c.c. of hydrogen at N.T.P., corresponding to I.V., 83·5. Calc. for monohydroxyoleic ester, $C_{19}H_{36}O_3$: I.V., 81·5). The saturated ester was isolated and then saponified by one hour's heating under reflux with a 10% solution of potassium hydroxide in methyl alcohol to yield the corresponding saturated acid, which was recrystallised from acetone. The recrystallised saturated acid (Found: C, 72·4; H, 11·9; Br, 0·0; A.V., 191·4. Calc. for $C_{18}H_{36}O_2$: C, 71·95; H, 12·1%; A.V., 186·5) (m. p. 68—69°), which was used for Langmuir trough experiments, gave a depression of m. p. in admixture with stearic acid. A portion of the recrystallised saturated acid was converted into the methyl ester (m. p. 40—41°) by reaction with diazomethane in ethereal solution [Found: *M* (Menzies–Wright ebullioscopic in benzene), 328. Calc. for $C_{19}H_{38}O_2$: *M*, 314·4).

Attempted Chromatography of Allyl Bromide.—Allyl bromide (2 g.) in ether (100 c.c.) was passed through a column of alumina (8″ × ¾″); evaporation of the filtrate yielded unchanged allyl bromide.

Attempted Chromatography of 3-Bromocyclohexene.—3-Bromocyclohexene (10 g.), made from cyclohexene by the method of Zielger *et al.* (*loc. cit.*), in light petroleum (100 c.c.; b. p. 40—60°), was passed down a column of alumina (20″ × ¾″). As the solution travelled down the column the alumina became warm and turned blue. The column was washed with a 2% solution of ethyl alcohol in light petroleum (500 c.c.) and the filtrate was evaporated to yield a viscous red-brown liquid (Found: C, 74·8; H, 8·6; Br, 13·6%), apparently of polymeric complexity.

Bromination of Ethyl Linoleate.—Ethyl linoleate (8·4 g., 0·0273 mole), prepared by debromination of tetrabromostearic acid (*Org. Synth.*, **22**, 45), and *N*-bromosuccinimide (5·1 g. containing 0·028 atom of reactive bromine) were heated under reflux with frequent shaking in redistilled "AnalaR" carbon tetrachloride (50 c.c.) on a water-bath for 4½ hours under a slow stream of nitrogen. Hydrogen bromide was evolved towards the end of the refluxing; the mixture was cooled and filtered at the water-pump, the filter being washed with three 10-c.c. portions of carbon tetrachloride. The filtrate was freed from solvent in a vacuum and left a brown oil (9·1 g.) (Found: Br, 13·6; I.V., 117. Calc. for $C_{20}H_{35}O_2Br$: Br, 20·7%; I.V., 131); $n_D^{25°}$ 1·4820. Ultra-violet spectroscopic examination indicated that 10·2% of conjugated triene compounds was present.

The brominated ester was also prepared under mild conditions following Teeter (*loc. cit.*): ethyl linoleate (10 g.; 0·0326 mole), *N*-bromosuccinimide (5·8 g. containing 0·0326 atom of reactive bromine), and benzene (10 c.c.) were heated together and stirred at 70—75° for 25 minutes. After cooling, light petroleum (20 c.c.) was added and the succinimide was filtered off; the filtrate was evaporated in a vacuum, leaving a brown oil (12·2 g.) (Found: Br, 19·2%; I.V., 111), $n_D^{25°}$ 1·4870, which gave on ultra-violet spectroscopic examination $\lambda_{max.}$ 258·0 mμ, $\varepsilon_{max.} = 5800$ (assuming $M = 387$). The oil was heated for one hour at 100° in a slow stream of nitrogen and then gave a band at 269 mμ, the intensity of which corresponded to the presence of 11·4% of conjugated triene compounds; the development of the 269 mμ absorption masked the original 258 mμ band.

Attempted Molecular Distillation of Bromolinoleic Ester.—Hydrogen bromide was evolved when the bromo-ester was heated at 100° in a pot still under 10^{-4} mm. pressure.

Bromination of Ethyl Linolenate.—Ethyl linolenate (10·6 g., 0·0345 mole), prepared by debromination of hexabromostearic acid (*Org. Synth.*, **22**, 82), and *N*-bromosuccinimide (6·2 g. containing 0·0345 atom of reactive bromine) were heated under reflux with frequent shaking in redistilled "AnalaR" carbon tetrachloride (52 c.c.) for 4 hours; a copious evolution of hydrogen bromide occurred during the last 3 hours. The product, recovered exactly as in the case of bromo-linoleic ester described above, was a dark brown liquid (13·4 g.) which could not be distilled under 10^{-4} pressure without decomposition.

Bromination of Linseed Oil.—Alkali-refined linseed oil (10 g., 0·0125 mole) (Found: I.V., 177; A.V., 0·7) and *N*-bromosuccinimide (12·7 g. containing 0·070 atom of reactive bromine) were heated in boiling carbon tetrachloride solution for 4 hours as in the previous brominations; a copious evolution of hydrogen bromide occurred during the last 3 hours. The product (12·6 g.) was a dark brown viscous liquid (Found: Br, 18·8%; I.V., 93·5) which dried overnight to a hard film when spread on flat aluminium panels.

Reaction of Brominated Linseed Oil with Alkali.—Brominated linseed oil (10 g.), obtained as described above, was heated under reflux on a water-bath with a 20% solution of potassium hydroxide in ethyl alcohol (50 c.c.) for one hour. The bulk of the alcohol was removed by distillation and the residual solution was poured into water, acidified, and ether-extracted to yield a semi-solid mixture of fatty acids (6 g.) [Found: Br, 0·98%; A.V., 185; I.V. (Wijs) 143; I.V. (by hydrogenation), 214]. Ultra-violet spectroscopic examination indicated that a total of 33% of conjugated compounds were present, *viz.*, diene, 13%; triene, 12%; tetraene, 8%.

Analyses are by Mr. C. Whalley, spectroscopic work by Mr. N. H. E. Ahlers, and Langmuir-trough experiments by Mrs. W. Ribchester.

One of us (J. D.) is indebted to the Government of India for the tenure of an Overseas Scholarship. The above investigation forms parts of a programme of fundamental research carried out at the Paint Research Station, Teddington, and thanks are expressed to the Director and Council for permission to publish the results.

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203. *Effects of Solvents and Structure on the Thermal Transformation of* cis- *into* trans-*Diazocyanides.*

By R. J. W. LE FÈVRE and (MISS) J. NORTHCOTT.

The rates of thermal *cis–trans*-interconversion of ten diazocyanides in one solvent (benzene), and of one diazocyanide (*p*-chlorobenzenediazocyanide) in eight different solvents, have been compared. The reactions show first-order kinetics with frequency factors between 10^{12} and 10^{15} sec.$^{-1}$, and energies of activation from 21 to 26 kcals./g.-mol. The lower A and E values apply in the case of non-polar solvents, changing to the higher as the polarity of the solvent increases. No regular correlation of either k or E with solvent properties can be discerned. For various diazocyanides in benzene the influence of substituents can be expressed by the equation: $E = E_0 + 2{\cdot}9RT(\mu + 0{\cdot}209\mu^2)$, where E_0 is the energy of activation observed for benzenediazocyanide, and μ is the dipole moment of the appropriate C_6H_5X compound.

REACTIONS which proceed by first-order kinetics *in solution* have hitherto received rather infrequent attention (cf. Moelwyn-Hughes, " Kinetics of Reactions in Solution," Oxford, 1933), and of the cases reported the most numerous conform to the type A = B + C [*e.g.*, decompositions of diazonium or sulphonium salts, carboxylic acids, etc. (*op. cit.*, pp. 156, 157)]. Before 1938, direct *cis-* to *trans*-geometrical inversions had been studied only in the *gaseous* phase (Kistiakowsky and associates, various papers; *e.g.*, *J. Amer. Chem. Soc.*, 1935, **57**, 269), with the one exception of certain oxime inversions (*J.*, 1908, **93**, 1041; 1912, **101**, 26, 2100; 1941, 606) which Patterson and his co-workers had followed polarimetrically in mixed solvents containing ethyl tartrate.

Ten years ago, as a side issue to their structural investigation, the isomeric diazocyanides and azobenzenes (Le Fèvre and Vine, *J.*, 1938, 431; Hartley, *ibid.*, p. 633; Le Fèvre and Hartley, *ibid.*, 1939, 531) were found to undergo interconversion in organic solvents at rates that could be conveniently measured either dielectrically or photometrically. The opportunity was therefore taken to commence the examination of the rôles of substituents and media in reactions involving the $-N{=}N-$ group.

By August, 1939, when the work had to be suspended, preliminary surveys (with Vine and Saboor, Ph.D. Theses, London, 1938 and 1941, respectively; Saboor, *Indian J. Physics*, 1943, **17**, 223) had satisfactorily indicated that, in a number of solvents, the time of half-change was generally independent of the initial concentration of the less stable form; *i.e.*, the reactions were apparently of the first order. The k values could therefore be obtained from the times of half change read from a dielectric constant–time curve.

This paper records the comparison of ten diazocyanides in one solvent (benzene), and of one (*p*-chlorobenzenediazocyanide) in eight different solvents.

In some instances, *slight* indications have been found of " initial disturbances." It is difficult to decide whether these arise from experimental errors near the beginning of a " run ", or from the fact that the isomerisation really involves a pair of consecutive changes (*e.g.*, *cis* $\xrightarrow{k_1}$ active intermediate $\xrightarrow{k_2}$ *trans*, in which k_2 is the rate-determining factor). The latter is a possibility, but (compare Walker, *Proc. Roy. Soc. Edin.*, 1898, **22**, 23) *unless* k_1 and k_2 are widely different in magnitude, " first-order kinetics " cannot appear, and *if* the separate constants *are* widely different, the rate-determining constant and the " overall " (observed) constant will be practically undistinguishable.

Our measurements are summarised in Table I.

Discussion.—As a preliminary we have evaluated, from the data in Table I, the frequency factors (A) and the energies of activation (E) from the equation $k = Ae^{-E/RT}$. The results are shown in Table II. For the thermal *cis-* to *trans*-conversion of azobenzene, either alone (fused) or dissolved in acetone or benzene, Hartley (*loc. cit.*) records a mean activation energy of 23 kcals./g.-mol., and for the *p*-dimethylamino-derivative, a value 2 kcals./g.-mol. lower. The similarity between the diazocyanides and azobenzene is therefore clear. It is accordingly of interest to compare the data of Table II with the studies, mentioned above, of analogous

TABLE I.

Thermal isomerisation of cis-*aromatic diazocyanides.*

Diazocyanide.	Solvent.	k^{25} (hr.$^{-1}$).	k^{45} (hr.$^{-1}$).	k^{x} (hr.$^{-1}$).
Benzene-	C_6H_6	5·55	—	1·43 (15°)
p-Toluene-	C_6H_6	4·12	—	1·03 (15°)
α-Naphthalene-	C_6H_6	0·224	2·568	—
β-Naphthalene-	C_6H_6	0·165	1·926	—
p-Chlorobenzene-	$C_6H_{10}O$ *	0·015$_5$	0·25	—
,,	C_5H_5N	0·029	0·46	—
,,	*o*-$C_6H_4Cl_2$	0·041	0·58	—
,,	C_6H_6	0·065	0·63	—
,,	$CHCl_3$	0·074$_5$	0·73	—
,,	CCl_4	0·071	0·77	—
,,	C_6H_{12} †	0·084$_5$	0·87	—
,,	C_6H_5Cl	0·078	0·99	—
p-Bromobenzene-	C_6H_6	0·058	—	2·08 (57·5°)
o- ,,	C_6H_6	0·028	—	—
p-Nitrobenzene-	C_6H_6	0·026	0·27	—
p-Methoxybenzene-	C_6H_6	3·47	—	0·97 (15°)
2 : 4 : 6-Tribromobenzene-	C_6H_6	—	—	0·11 (57·5°) 0·396 (70·0°)

* *cyclo*Hexanone. † *cyclo*Hexane.

TABLE II.

Diazocyanide.	Solvent.	A (sec.$^{-1}$).	E. (kcals./g.-mol.).
Benzene-	C_6H_6	*ca.* 1 × 10^{15}	23·0
p-Toluene-	C_6H_6	*ca.* 2 × 10^{15}	23·5$_5$
α-Naphthalene-	C_6H_6	5 × 10^{13}	22·9
β-Naphthalene-	C_6H_6	4 × 10^{13}	23·1
p-Chlorobenzene-	$C_6H_{10}O$	6·8 × 10^{14}	26·1
,,	C_5H_5N	1·0 × 10^{15}	25·9$_5$
,,	*o*-$C_6H_4Cl_2$	2·2 × 10^{14}	24·9
,,	C_6H_6	9·5 × 10^{11}	21·3$_5$
,,	$CHCl_3$	1·2 × 10^{12}	21·4
,,	CCl_4	5·5 × 10^{12}	22·4
,,	C_6H_{12}	3·2 × 10^{12}	21·9
,,	C_6H_5Cl	7·1 × 10^{12}	23·8$_5$
p-Bromobenzene-	C_6H_6	1·5 × 10^{12}	21·6
p-Nitrobenzene-	C_6H_6	*ca.* 1 × 10^{12}	21·9$_5$
p-Methoxybenzene-	C_6H_6	*ca.* 3 × 10^{13}	21·7
2 : 4 : 6-Tribromobenzene-	C_6H_6	5·6 × 10^{11}	23·0

geometrical changes in the gaseous phase of such molecules as maleic ester, *cis*-but-2-ene, *cis*-methyl cinnamate, *cis*-stilbene, and its mono-and dichloro-derivatives (see Moelwyn-Hughes, *op. cit.*, Chap. II, for summary). Our results at once suggest a marked contrast between the $-N{=}N-$ and the $-C{\equiv}C-$ containing compounds, since for the latter the reactions appear to fall into two groups distinguished by their A and E values. In the first, these quantities are around 10^{14} sec.$^{-1}$ and 25 kcals./g.-mol., while in the second, the corresponding data are *ca.* 10^{11} and 45. The dissolved diazocyanides (and azobenzene, so far as data exist) are thus found to be intermediate, in that their frequency factors range from 10^{12} to 10^{15} sec.$^{-1}$ and their energies of activation from 21 to 26 kcals./g.-mol. It is possible that the distinction just emphasised would be understandable by a theoretical treatment similar to that sketched for the ethylenic case by Glasstone, Laidler, and Eyring ("The Theory of Rate Processes," McGraw-Hill, 1941, 325) but at present this cannot be applied since the torsional frequency for the $-N{=}N-$ system is unavailable.

We therefore restrict our discussion to (*a*) the effects of solvents on the *cis–trans-p*-chlorobenzenediazocyanide change, and (*b*) the effects of substituent groups on the *cis–trans*-benzenediazocyanide change.

Effects of Solvents.—A number of attempts to correlate the influences of different solvents on particular reactions, with certain physical properties of the solvent or of the solution, are on record (cf. Moelwyn-Hughes, *op. cit.*, Chap. VI). The literature shows, however, that the relative velocities of a given reaction in a series of solvents are seldom reproduced for a different chemical reaction in the same media. This seems to be true both for the A = B + C decomposition type and the A = B molecular rearrangement type (*e.g.*, camphene hydrochloride to *iso*bornyl chloride, Meerwein *et al.*, *Ber.*, 1922, **55**, 2507; *Annalen*, 1924, **435**, 211; also the racemisation—compare, however, Conant and Carlson, *J. Amer. Chem. Soc.*, 1929, **51**, 3464;

Savich and Goldblatt, *ibid.*, 1945, **67**, 2027—of *d*-pinene, Smith, *ibid.*, 1927, **49**, 43, etc.) for which the degree of solvent dependency is variable, sometimes marked, but sometimes nil (as in Smith's case; or the thermal breakdown of dinitrogen pentoxide, Eyring and Daniels, *ibid.*, 1930, **52**, 1472).

To set our results against this background, we note that *cis*-*p*-chlorobenzenediazocyanide isomerises at about the same speed in carbon tetrachloride as in chloroform, while Beckmann changes of the picryl ethers of benzophenone and acetophenone oximes (which likewise proceed spontaneously in pure solvents, and by first-order kinetics, Chapman and Howis, *J.*, 1933, 806) have rates which are *much* less in the former solvent than in the latter.

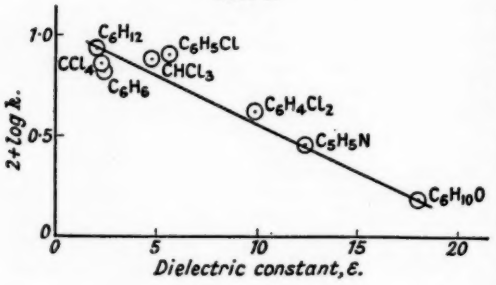
Even towards two closely similar reactions [*e.g.*, the formation of $(Et_4N)Br$ and $(Et_4N)I$; cf. Mellor, "Chemical Statics and Dynamics", Longmans, 1909, 341] the catalytic powers of a series of liquids may not be quantitatively the same. It is accordingly not surprising that our observed orders for 25° and 45° should differ:

at 25°: *cyclo*hexane>C_6H_5Cl>$CHCl_3$>CCl_4>C_6H_6>*o*-$C_6H_4Cl_2$>C_5H_5N>*cyclo*hexanone

at 45°: C_6H_5Cl>*cyclo*hexane>CCl_4>$CHCl_3$>C_6H_6>*o*-$C_6H_4Cl_2$>C_5H_5N>*cyclo*hexanone

In the circumstances, therefore, one can scarcely expect to establish a quantitative correlation between reaction velocity and any *one* solvent property. Where, in the past, apparent relationships have been noticed, some mechanistic feature has often been obvious (*e.g.*, ionisation, where k has varied with the dielectric constant, as in the decomposition of sulphonium salts, von Halban, *Z. physikal. Chem.*, 1909, **67**, 129; or cohesion, where an effect of surface tension has been traced, as in the interactions between *N*-chloroacetanilide and hydrochloric acid solutions, Richardson and Soper, *J.*, 1929, 1873). No such guide is provided by the various attempts to describe a model for configurational inversion about a double bond.

FIG. 1.



Nevertheless, in addition to what follows we have also explored the variation of k and log k with such single solvent properties as viscosity, surface tension, refractive index, molecular and specific refraction, specific dispersion, the coefficient of cubical expansion, cohesion, adiabatic compressibility, internal pressure, parachor, etc. In most cases the absence of a correlation has been clearly visible merely by inspection. The failure with viscosity is significant since the number of collisions between solvent and solute, by simple theory, is $Z = 3\pi\eta\sigma/2m_1$ (cf. Moelwyn-Hughes, *op. cit.*, p. 28), where σ/m_1 refers to the *solute*. Yet there is no relation between A (Table II) and Z as calculated from η. Taking the effective diameter of *p*-chlorobenzenediazocyanide to be probably between 6 and 12 A. (see later), we find that the observed A is always less than Z by the above formula. The introduction (Hinshelwood, "Kinetics of Chemical Change," Oxford, 1940, 51) of a temperature-invariant factor, P, to represent various unknown conditions modifying Z, would qualitatively rationalise the situation.

The literature contains many references suggesting that connections between reaction velocities and properties are commonly very indirect. The empirical rule of Richardson and Soper (*loc. cit.*) may be cited as one example, and if in our cases the assumption may be made that the transition state resembles the product (as it probably does), but exceeds it in internal pressure, then solvents of high internal pressure should act deceleratively if the second phase of the overall reaction is the rate-determining stage. (Activated, and polar, intermediate forms, *e.g.*, $X{\cdot}\overset{+}{C}_6H_4{\cdot}\overset{\cdot\cdot}{N}{\cdot}\overset{-}{N}{\cdot}CN$, *may* be involved; their moments would be many multiples of those of the *trans*-form which, *e.g.*, when X = Cl, has $\mu = 3{\cdot}7$ D.) Since internal pressure runs roughly parallel to the dielectric constant of a liquid, it is notable that, qualitatively, a general slowing of reaction does in fact seem to accompany a gross increase in the dielectric constant of the medium (compare the speed in *cyclo*hexanone, $\varepsilon = 18$, with that in *cyclo*hexane, $\varepsilon = 2$), although the corresponding rates in benzene, chloroform, carbon tetrachloride, and chlorobenzene ($\varepsilon = 2{\cdot}3, 4{\cdot}7, 2{\cdot}2, 5{\cdot}6$, respectively) clearly indicate that no *accurate* parallelism with this property exists. However, a graph of log k against $\varepsilon_{solvent}$ (Fig. 1) reveals an *approach* to a smooth relationship.

A number of authors have attempted to consider liquid-phase reactions in the light of a

quasi-crystalline structure of liquids. Bradley (*J.*, 1934, 1910) assumes a spherical solute molecule, surrounded by 12 others, within which the motion of the central one resembles a high-frequency vibration with a continually changing axis. If v^2 is the mean square velocity of the solute and α its amplitude of vibration, then, for a unimolecular reaction $k = \frac{v}{\alpha}\left(\frac{3\pi}{2}\right)^{\frac{1}{2}}\frac{E}{RT}e^{-E/RT}$. The quantity α might therefore be related to the interstitial spaces in the models of the various solvents; Bradley (*Trans. Faraday Soc.*, 1937, **33**, 1185) equates it to $2(2{\cdot}22/4\pi N)^{\frac{1}{3}}(V^{\frac{1}{3}} - V_0^{\frac{1}{3}})$, where V and V_0 are the molecular volumes at $T°$ and the absolute zero, respectively. Using Sugden's data (*J.*, 1927, 1786) we have computed $(V^{\frac{1}{3}} - V_0^{\frac{1}{3}})$, but find no proportionality between $E_{obs.}/(V^{\frac{1}{3}} - V_0^{\frac{1}{3}})$ and A (Table II). In combination, however, with the independent approach by Wheeler (*Proc. Indian Acad. Sci.*, 1936, **4**, 291), Bradley's α becomes $0{\cdot}268(kT/r)(V/P)^4$, where P = parachor, r = solvent radius, which (for a hexagonally close-packed arrangement) $= (\frac{3}{4}0{\cdot}74M/N\pi d)^{\frac{1}{3}} = (0{\cdot}2916V)^{\frac{1}{3}} \times 10^{-8}$ cm. Again, however, the solvents are not placed in their correct frequency factor order.

Waring and Becher (*J. Chem. Physics*, 1947, **15**, 488) assign a vibrational frequency, f, to the molecules of the solvent " crystal ", and calculate f as $C(3N/4\pi V)^{\frac{1}{3}}$, where C is the velocity of sound in the medium, and V the molecular volume. The reaction constant is given by

$$k = \frac{nf}{(S-1)!}\left(\frac{E_g}{RT}\right)^{S-1}(e^{-E_{obs.}/RT})$$

n being the number of molecules surrounding the solute, S the specified number of internal degrees of freedom contributing to the reaction, and E_g the theoretical energy of activation of the reaction in the gaseous phase. Thus according to this theory the logarithms of the observed frequency factors, listed in Table II, should be proportional to (log C − 0·5 log V + log n + constants). We have estimated n in two ways as follows: (i) A scale drawing showed that *cis-p*-chlorobenzenediazocyanide may reasonably be fitted into a prolate spheroid whose major axis ($2a$) is twice its minor. The ratio (molecular volume at 25°)/parachor is roughly 0·45 [this is a fortuitous relation; cf. Sugden, *J.*, 1927, 1780, *re* the analogous apparent relationships between zero and molecular volumes—since Parachor = (molecular volume)(surface tension)$^{\frac{1}{4}}$, and for most organic liquids the surface-tension range is small]. The parachor of *p*-chlorobenzenediazocyanide is about 350 (measured, see Experimental; 342 calculated) whence $V_{25°} = ca.$ 158, and $158/(6{\cdot}06 \times 10^{23}) = \pi a^3/3$, whence $a = 6{\cdot}29$ A. Using the virtual radii of the solvents (cf. above) we next evaluated the surface areas of spheroids in which the axes were $2(6{\cdot}29 + r_{solvent})$ and $2(3{\cdot}14_5 + r_{solvent})$, respectively. Division by $2\sqrt{3}\,r^2_{solvent}$ provided n. (ii) As above, except that n was taken as Area/$4r^2$. The results are compared in Table III.

TABLE III.

Estimated numbers of solvent molecules surrounding p-*chlorobenzenediazocyanide.*

	(i).	(ii).		(i).	(ii).
*cyclo*Hexanone	19·7	17·1	$CHCl_3$	21·6	18·7
Pyridine	21·6	18·7	CCl_4	20·2	17·5
o-$Cl_2C_6H_4$	19·2	16·6	*cyclo*Hexane	19·4	16·8
C_6H_6	20·9	18·1	C_6H_5Cl	19·9	17·2

TABLE IV.

Observed.	*ex* Bradley.	*ex* Wheeler.	*ex* Waring & Becher.
C_5H_5N	*o*-$C_6H_4Cl_2$	*o*-$C_6H_4Cl_2$	C_5H_5N
*cyclo*Hexanone	*cyclo*Hexanone	*cyclo*Hexanone	C_6H_6
o-$C_6H_4Cl_2$	C_6H_5Cl	C_5H_5N	*cyclo*Hexanone
C_6H_5Cl	C_5H_5N	C_6H_5Cl	C_6H_5Cl
CCl_4	$CHCl_3$	C_6H_6	$CHCl_3$
*cyclo*Hexane	C_6H_6	CCl_4	*cyclo*Hexane
$CHCl_3$	CCl_4	*cyclo*Hexane	*o*-$C_6H_4Cl_2$
C_6H_6	*cyclo*Hexane	$CHCl_3$	CCl_4

The number varies from 17 to 22; it is considerably more than the 12 adopted by Bradley.

When the appropriate measurements (velocity of sound data from Freyer, Hubbard, and Andrews, *J. Amer. Chem. Soc.*, 1929, **51**, 759; Willard, *J. Acoustic Soc. Amer.*, 1941, **12**, 438; and Bergman, " Ultrasonics ", transl. Hatfield, Wiley, 1939) are introduced into the various expressions, the solvents may be arranged (Table IV) in descending orders of the relative frequency factors forecast. Not only is the experimental sequence not followed, but the

calculated quantities are not " spread " nearly sufficiently. A similarly inappropriate result is obtained if the estimated surfaces of the solute ellipsoids (above) are multiplied by the number of solvent molecules striking a unit area per second; *i.e.*, $d_S N/M_S(RT/2\pi M_S)^{\frac{1}{2}}$ (cf. Moelwyn-Hughes, *op. cit.*, p. 28)—an approach which, because of the relative size of the solute, seems *a priori* reasonable.

Glasstone, Laidler, and Eyring (*op. cit.*, p. 420) point out that in certain cases log k has varied with $(\varepsilon - 1)/(2\varepsilon + 1)$, rather than with ε directly (as attempted in Fig. 1). Fig. 2 shows signs of a correlation on this basis *except for the three solvents* whose molecules are ordinarily regarded as non-polar. The position of C_6H_5Cl ($\mu = 1{\cdot}6$ D.) relatively to CCl_4 ($\mu = 0$), C_6H_6 ($\mu = 0$), etc., in Table I negatives an immediate connection with solvent moments as usually measured. We note, however, that Fig. 3, in which $E_{obs.}$ is shown against ε, brings the two solvent types more nearly on to one line. Moreover, the solute has an appreciable polarity ($\mu = 2{\cdot}9 - 3{\cdot}7$ D. in C_6H_6; Le Fèvre and Vine, *loc. cit.*); it will induce polarity in the surrounding solvent molecules, and hold them by electrostatic attractive forces. Since the latter may need

FIG. 2.

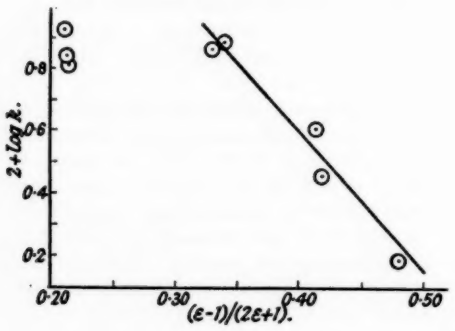
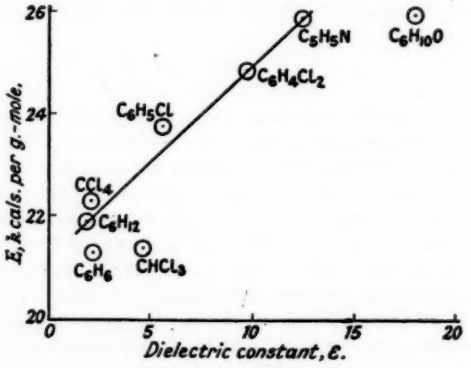


FIG. 3.



to be overcome during the inversion reaction, some influence, probably on the activation energy, could intuitively be foreseen. This possibility has been explored with the following assumptions: The solute dipole (3 D.) is situated at an average distance = 4·72 A. (*i.e.*, the mean of the major and minor half-axes mentioned above) plus $r_{solvent}$ (calculated from the molecular volumes at 25°; cf. Table VII) from the centres of the surrounding solvent molecules, whose polarisabilities are given by $\alpha = 0{\cdot}0394[R_L]_D \times 10^{-23}$ c.c. The maximum moment, μ_M, acting anti-parallel to μ_{solute}, of each solvent molecule is therefore *ca.* $\mu_{solvent} + 2(\alpha_{solvent}\,\mu_{solute})/(4{\cdot}72 + r_{solvent})^3$. The interaction energy U (cf. Jeans, " Electricity and Magnetism," Cambridge Univ. Press, 1920,

TABLE V.

	μ, D.	$\alpha \times 10^{23}$.	$\mu_M \times 10^{18}$.	$U \times 10^{15}$.	$Q^2U \times 10^{15}$.
*cyclo*Hexanone	2·8	1·09	2·94	18·3	32·4
C_5H_5N	2·3	0·95	2·43	16·7	30·4
o-$Cl_2C_6H_4$	2·3	1·36	2·46	14·8	27·8
C_6H_6	0	1·03	0·14	0·93	1·2
$CHCl_3$	1·0	0·84	1·12	7·7	11·5
CCl_4	0	1·04	0·13	0·83	1·1
*cyclo*Hexane	0	1·09	0·13	0·80	1·0
C_6H_5Cl	1·6	1·22	1·75	11·0	18·6

354) is therefore proportional to $\mu_M \cdot \mu_{solute}/(4{\cdot}72 + r_{solvent})^3$. In the last but one column of Table V are shown the values of U which are plotted against $E_{obs.}$ (*ex* Table II) in Fig. 4.

The result is promising. It will be noted that both polar and non-polar solvents whose molecular shapes are related tend to lie on a straight line. Chloroform shows the greatest disagreement, but since it may aggregate itself around the solute by the three chlorine atoms, its resultant moment might never act co-linearly with that of the diazocyanide; thus the fundamental assumption made above is least applicable in this case. Perhaps the " actual " dipole moments (when surrounded by other molecules in the liquid state) should be considered. Onsager (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) calculates them by $\mu_{actual}/\mu_{gas} = (n^2_\infty + 2)(2\varepsilon + 1)/3(2\varepsilon + n^2_\infty) = Q$. We have evaluated Q for each solvent (using n_D as an

approximation to n_∞; see Table VII) and roughly corrected the U values (Table V) by multiplying by Q^2. The effect may be seen by comparing Figs. 4 and 5.

FIG. 4.

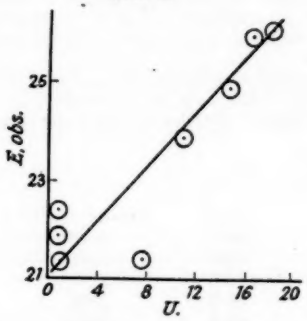
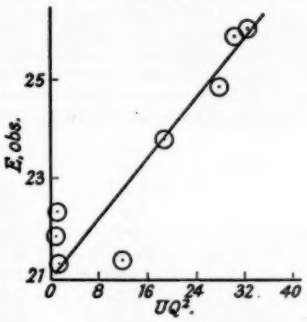


FIG. 5.



Possibility of Adventitious Catalysis.—In view of the demonstration that molecular oxygen can catalyse certain *cis* ⟶ *trans*-reactions in C=C systems (Tamamushi and Akiyama, *Z. Electrochem.*, 1937, **43**, 156) or C=N systems (Taylor and Lavington, *J.*, 1934, 980), it should be pointed out that no such effect is apparent in our experiments. The observed rates are the same in freshly vacuum-distilled solvents as in those which have been standing in contact with air for several weeks, and the order of velocities shown in Table I is quite different from that shown in the International Critical Tables (Vol. III, p. 262) for the solubilities of oxygen in the eight solvents used.

Effects of Substituents.—Because of the conclusions of Brönsted and Pederson (*Z. physikal. Chem.*, 1924, **108**, 185; compare Hinshelwood, *J.*, 1937, 635, and Hammett, *Chem. Reviews*, 1935, **17**, 125; *Trans. Faraday Soc.*, 1938, **34**, 156), a relation was first sought between log k (from Table I) and log K_A, where the latter refers to the dissociation constants of *p*-substituted benzoic acids. On the whole the two sets of values indicate a definite drift. We next attempted the correlation noted by Waters (*Phil. Mag.*, 1929, **8**, 436) and Nathan and Watson (*J.*, 1933, 893), who succeeded in expressing in an approximately linear manner the dipole moments of certain benzene derivatives C_6H_5X with the logarithms of the dissociation constants of various benzoic and acetic acids. This was tolerably successful, but a better fit is obtained by the general equation (Waters, *J.*, 1933, 1551; *Nature*, 1934, **134**, 178; Watson, *Trans. Faraday Soc.*, 1938, **34**, 165): $E = E_0 \pm C(\mu + \alpha\mu^2)$. The values of E listed in Table II for the *p*-chloro-, *p*-nitro-, and unsubstituted benzenediazocyanides being used, values of $\alpha = 0{\cdot}209$ and $C = 1604$ lead to good agreement between found and calculated values for the energies of activation. The moments of the corresponding $C_6H_5{\cdot}X$ are shown in col. 2 of Table VI.

TABLE VI.

Diazocyanide.	μ(D.).	E (kcals./g.-mol.). calc.	found.
Benzene-	0	23·0	23·0
p-Toluene-	+0·34	$23{\cdot}5_8$	$23{\cdot}5_5$
p-Chlorobenzene-	−1·5	$21{\cdot}3_5$	$21{\cdot}3_5$
p-Nitrobenzene-	−4·0	$21{\cdot}9_5$	$21{\cdot}9_5$
p-Methoxybenzene-	−1·23	$21{\cdot}5_2$	21·7
2 : 4 : 6-Tribromobenzene-	0	23·0	23·0

Nathan and Watson (*J.*, 1933, 890; *Nature*, 1934, **133**, 379; Evans, Morgan, and Watson, *J.*, 1936, 1174) write their equation for the substituted acetic acid case as $E = E_0 + 2{\cdot}4RT(\mu + 0{\cdot}032\mu^2)$. Expressing our results in the same form, we have $E = E_0 + 2{\cdot}9RT(\mu + 0{\cdot}209\mu^2)$.

EXPERIMENTAL.

Solutes.—These were prepared by methods described in earlier papers (Anderson, Le Fèvre, and Savage, *J.*, 1947, 445; Anderson, Bedwell, and Le Fèvre, *ibid.*, p. 457; Le Fèvre and Northcott, this vol., p. 333).

Solvents.—" Thiophen-free " benzene was dried, partially frozen in contact with sodium wire, and decanted; the solid portion remaining, after remelting, was stored over sodium. Carbon tetrachloride was shaken with mercury, washed successively with concentrated sulphuric acid, dilute sodium hydroxide, and water, then dried ($CaCl_2$) and distilled under moderately reduced pressure immediately before use, b. p. 26°/120 mm. Chloroform (A.R.), stored in contact with calcium chloride, was distilled when

required, b. p. 28·1°/225 mm. *cyclo*Hexane, purified as above for benzene, had b. p. 81°/760 mm. *cyclo*Hexanone was first precipitated as the bisulphite compound which, after separation, was decomposed by sodium carbonate solution; the liberated ketone, after steam-distillation and drying (Na_2SO_4), was redistilled; b. p. 155·5°/760 mm. Pyridine was kept over potassium hydroxide for several days, then twice boiled under reflux with fresh pellets of potassium hydroxide; it was fractionated as needed; b. p. 115°/759 mm. *o*-Dichlorobenzene was partially frozen, etc., then distilled, and only the middle fraction taken; this was stored over calcium chloride; b. p. 86°/18 mm. A pure stock of chlorobenzene was dried ($CaCl_2$) and redistilled as necessary; b. p. 132°/762 mm.

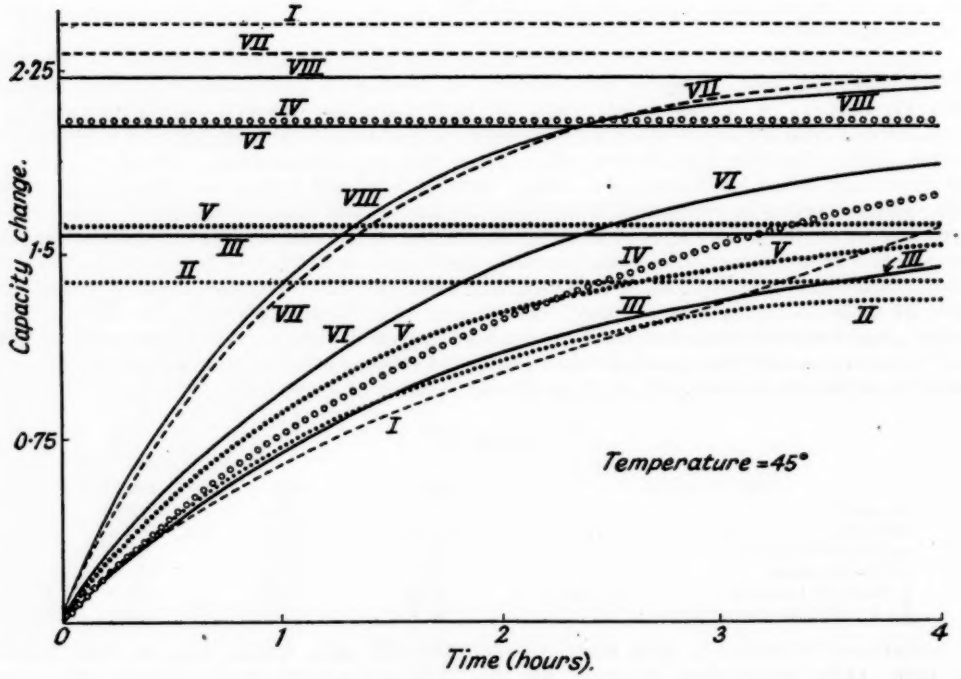
In most cases the densities and refractive indexes, and in some cases the dielectric constants (relative to benzene or chloroform), of these solvents have been checked. The data are assembled in Table VII, together with the molecular volumes, solvent radii, and " Onsager " factors (Q) used previously in this paper.

TABLE VII.

	$\varepsilon_{25°}$.	$[n_D^2]_{25°}$.	$d_4^{25°}$.	$V_{25°}$.	$(r_{solvent}) \times 10^8$.	Q.
*cyclo*Hexanone	18·2	2·1031	0·9411	104·1	3·12	1·33
C_5H_5N	12·4	2·2720	0·9773	80·8	2·87	1·35
o-$Cl_2C_6H_4$	9·82	2·3951	1·2934	113·6	3·21	1·37
C_6H_6	2·27 *	2·2420	0·8738	89·3	2·96	1·15
$CHCl_3$	4·72 †	2·0825	1·4790	80·7	2·87	1·23
CCl_4	2·23	2·1656	1·5855	97·0	3·05	1·15
*cyclo*Hexane	2·04	2·0221	0·7740	108·5	3·16	1·12
C_6H_5Cl	5·61 ‡	2·3180	1·1012	102·1	3·10	1·30

* Hartshorn and Oliver, *Proc. Roy. Soc.*, 1929, **123**, 664.
† Ball, *J.*, 1930, 570. ‡ Sugden, *J.*, 1933, 768.

FIG. 6.



Curve No.	Solvent.	Total capacity change.*	Curve No.	Solvent.	Total capacity change.*
I	*cyclo*Hexanone	2·43	V	Carbon tetrachloride	1·60
II	Chloroform	1·38	VI	Benzene	2·02
III	*o*-Dichlorobenzene	1·58	VII	*cyclo*Hexane	2·22
IV	Pyridine	2·04	VIII	Chlorobenzene	2·30

* In arbitrary units of a micrometer drive (see Le Fèvre and Northcott, *loc. cit.*).

Apparatus and Procedure.—The essential modifications to standard practice have already been noted (Le Fèvre and Northcott, *loc. cit.*). The thermostat liquids (paraffin) were in all cases dyed a deep red.

The formal justification for the use of the dielectric constant as an index of the progress of these reactions lies in the fact that, for each of some 16 diazocyanides hitherto examined, this property has had a rectilinear dependence upon concentration, so that, *e.g.*, $\varepsilon_{12} = \varepsilon_2(1 + \alpha w_{cis})$ for one form, or $\varepsilon_2(1 + \gamma w_{trans})$ for the other. Starting at t(time) = 0 with a weight fraction S of *cis*-isomer, after a given time interval a weight fraction x of the *trans*-isomer has been formed. Then $(\varepsilon_{12})_t = \varepsilon_2 + \alpha\varepsilon_2 S + x\varepsilon_2(\gamma - \alpha)$, *i.e.*, x is linear with ε_{12}. Since changes in the latter are compensated by adjustments of a parallel timing capacity, the rates have been, in fact, plotted as capacity–time curves, from which the times of half change can be read directly. Fig. 6 is reproduced as a specimen of our results.

As examples of the non-dependence of the times of half-change ($t_{\frac{1}{2}}$) upon concentration the following figures for *p*-chlorobenzenediazocyanide at 45° may be quoted :

$10^5 w_1$.	Solvent.	$t_{\frac{1}{2}}$, mins.	$10^5 w_1$.	Solvent.	$t_{\frac{1}{2}}$, mins.	$10^5 w_1$.	Solvent.	$t_{\frac{1}{2}}$, mins.
438	C_6H_6	69	845	C_6H_5Cl	39	1592	C_5H_5N	90
1258		66	1886		42	2380		90
1667		66	2458		42	2967		89

To indicate the extent of the "initial disturbances" (cf. p. 944) we compare below, for typical runs (of the *p*-chloro-derivative at 45°) the k values calculated at stated time intervals with those obtained by reading $t_{\frac{1}{2}}$ from a smoothed curve incorporating numerous actual observations :

Time, mins.	*cyclo*-Hexanone.	C_5H_5N.	*o*-$Cl_2C_6H_4$.	Solvent. C_6H_6.	$CHCl_3$.	CCl_4.	*cyclo*-Hexane.	C_6H_5Cl.
5	0·360	0·478	0·597	0·992	0·719	0·778	0·865	0·956
15	0·334	0·483	0·542	0·690	0·730	0·777	0·870	1·02
30	0·309	0·461	0·584	0·636	0·726	0·779	0·881	0·995
60	0·256	0·458	0·585	0·636	0·713	0·772	0·874	0·996
90	0·255	0·462	0·582	0·635	0·732	0·775	0·873	0·994
120	0·255	0·462	0·586	0·632	0·715	0·774	0·875	1·00
190	0·254	0·462	0·577	—	0·734	0·768	0·868	1·00
240	0·258	0·463	0·589	0·634	0·732	0·769	0·873	0·99
360	0·250	—	—	—	—	—	—	—
480	0·248	—	—	—	—	—	—	—
k from $t_{\frac{1}{2}}$	0·25	0·46	0·58	0·63	0·73	0·77	0·87	0·99

Parachors.—Benzene solutions of *p*-chloro- and 2 : 4 : 6-tribromo-benzenediazocyanides at 25° were examined by the procedure of Hammick and Andrew (*J.*, 1929, 754; cf. Sugden, *ibid.*, 1924, **125**, 27). Owing to solubility limitations, concentrations greater than mol.-fraction = 0·004 could not be used and $(P)_{obs.}$ was therefore uncertain; *e.g.*, for the two solutes named, values of (*a*) 347, 356, 358 and (*b*) 453, 461 were recorded respectively. The corresponding calculated figures are 342 and 456. Attempts to estimate the molecular surface areas (from $-\mathrm{d}\gamma/\mathrm{d}\log C$; Gibbs's equation) were unsatisfactory because the results (32—55 A^2) did not enable us to check the dimensions used in discussion above (p. 947).

General Note.—In the course of recent discussions on diazocyanides in *Chemistry and Industry* [1948, 158 (Calderbank, Le Fèvre, and Northcott), 270 (Hodgson), 301 (Waters), 732 (Le Fèvre, Northcott, and Wilson), 543 and 782 (Hodgson), 588 (Le Fèvre and Northcott)], Hodgson has questioned the purities of the stable and labile forms actually used in the various investigations with which we are concerned. He says "In my experience, the rate of conversion of many of these *cis*-diazocyanides is very rapid even below 0° . . ." and ". . . if I am right, all Professor Le Fèvre's work refers either to mixtures of *cis*- and *trans*-forms or to *trans*-forms only."

Our answer to these charges is largely based on the measurements now reported in detail for the first time. Pure solutes of sharp m. p. have always been used as starting materials, while the interval for half-change (at ordinary temperatures) of the substances upon which dipole-moment and infra-red observations were made, respectively, in 1938 and 1947, has never been *less* than 8 *hours*. We therefore feel confident that our past data, requiring only *minutes* for their collection, have been correctly ascribed, and that photo-equilibria, or changing mixtures of labile and stable isomers, have not been mistaken for either of the separate forms.

Note, added November 5th, 1948.—The authors are grateful to the Referees for the following further comment. ". . . the experiments made with *cis-p*-chlorobenzenediazocyanide in a wide range of solvents, including some like pyridine which would *immediately* combine with free ions (or radicals), give conclusive proof that this isomeric change is wholly intramolecular and does not involve any transient dissociation of the labile isomeride."

The stability of the system, and the quantitative yield of the *trans*-isomeride in all these solvents is also an argument for the rejection of an "*iso*nitrile" formulation.

Our thanks are due to the Chemical Society for permission to retain apparatus originally procured through one of its Research Grants, and to the Commonwealth Science Fund for financial assistance.

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N.S.W., AUSTRALIA.

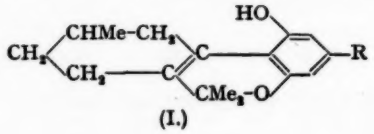
[*Received, September 13th*, 1948.]

204. *Tetrahydrodibenzopyran Derivatives Isomeric with Tetrahydrocannabinols.*

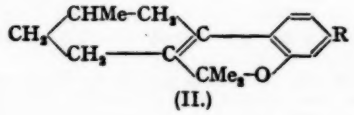
By A. W. D. Avison, A. L. Morrison, and M. W. Parkes.

A new series of tetrahydrodibenzopyran derivatives is described isomeric with that corresponding to synthetic tetrahydrocannabinol. Members of the new series are derived from 4- instead of 5-alkylresorcinols and are thus, in general, easier of access. Hashish activity, as measured by the Gayer test, is still present, but there is less pronounced change of potency with variation in the alkyl substituent. Attempts to prepare *sec.*-alkylresorcinols by direct alkylation of resorcinol are described.

The tetrahydrocannabinol (I; R = n-C_5H_{11}) was first synthesised by Ghosh, Todd, and Wilkinson (*J.*, 1940, 1121) and by Adams and Baker (*J. Amer. Chem. Soc.*, 1940, **62**, 2405). Homologues were also prepared (Russell, Todd, Wilkinson, MacDonald, and Woolfe, *J.*, 1941, 826; Adams, Loewe, Jelinek, and Wolff, *J. Amer. Chem. Soc.*, 1941, **63**, 1971), some of which showed greater pharmacological activity. In particular, the compound (I; R = n-C_6H_{13}), known as " Synhexyl " or " Parahexyl ", had the greatest activity as measured by dog-ataxia or rabbit corneal-areflexia (Gayer test) in the series where R is a straight carbon chain. Homologues where R contains branching alkyl groups vicinal to the aromatic ring were prepared by Adams and his group (*ibid.*, 1948, **70**, 662, 664; 1945, **67**, 1534) and found to exhibit extraordinarily high potencies (many times greater than those obtainable from natural sources) in the dog-ataxia test. Numerous attempts (Todd *et al.*, *J.*, 1941, 169, 826; Adams *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1973, 1977; 1942, **64**, 694, 2653) to vary the *cyclo*hexene or the pyran ring of the tetrahydrocannabinol structure resulted only in compounds having greatly



(I.)



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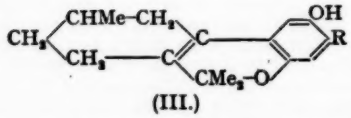

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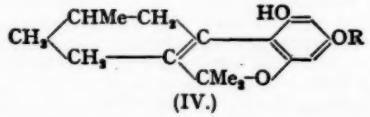


(IV.)

reduced activity, except in the case of hexahydrocannabinol. The only variations tried involving the aromatic ring were as in (II), (III), and (IV) derived from *m*-amylphenol, amylquinol, and phloroglucinol, respectively (Alles, Icke, and Feigen, *ibid.*, 1942, **64**, 2031; Russell, Todd, Wilkinson, MacDonald, and Woolfe, *J.*, 1941, 169; Bergel, Morrison, Rinderknecht, Todd, Macdonald, and Woolfe, *J.*, 1943, 286), no greater success in finding active compounds being achieved. Thus it appeared that only tetrahydrodibenzopyrans of the structure (I), their dihydro-compounds, and natural hemp drugs where the double bond is shifted, were capable of exhibiting hashish activity. However, those synthesised are all obtained only by a long route.

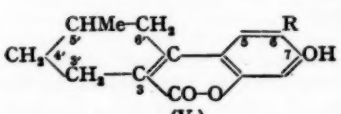
As " Synhexyl " has lately become of interest owing to its reported effect in depressive mental states (Tayleur-Stockings, *Brit. Med. J.*, 1947, 918), the search for active analogues, more easily prepared, is of some importance. The present paper reports some progress in this direction and shows that the specific arrangement of substituents in the tetrahydrocannabinol series is of less pharmacological significance than seemed likely hitherto.

When 4-n-hexylresorcinol was treated with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate and sulphuric acid, a *cyclo*hexenocoumarin was obtained. The structure of this compound was indicated, by its strong blue fluorescence in alkaline solution and failure to give a colour in the Gibbs test (*J. Biol. Chem.*, 1927, **72**, 649), to be the 7-*hydroxycoumarin* (V; R = n-C_6H_{13}).* This was confirmed by dehydrogenation with palladised charcoal to the *benzocoumarin* (VI), m. p. 220—222°, which was also synthesised from 2-bromo-4-methylbenzoic acid and 4-n-hexylresorcinol according to the method of Adams, Pease, Clark, and Baker (*J. Amer. Chem. Soc.*, 1940, **62**, 2197) (with 4-amylresorcinol it had been shown conclusively that condensation takes place in the 6-position; cf. Adams, Baker, *et al.*, *ibid.*, pp. 2201, 2204, 2208).

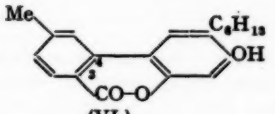
The coumarin (V; R = n-C_6H_{13}) was readily converted by the action of excess of methyl-

* The numbering of (V)—(VII) is that used in earlier papers by Todd and his co-workers.—Ed.

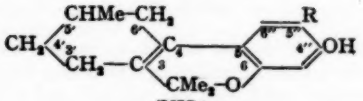
magnesium iodide in the usual way into the corresponding *4''-hydroxy-2 : 2 : 5'-trimethyl-5''-n-hexyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran* (VII; R = *n*-C_6H_{13}). The coumarins from 4-*n*-heptyl- and 4-*n*-octyl-resorcinol were prepared by using sulphuric acid or phosphorus oxychloride and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate. These were converted without any difficulty into the *tetrahydrodibenzopyrans* (VII; R = *n*-C_7H_{15}) and (VII; R = *n*-C_8H_{17}), respectively. Besides these three *n*-alkyl compounds, we prepared (VII; R = *cyclo*hexyl) from 4-*cyclo*hexylresorcinol. The latter is of interest since there is a secondary carbon atom next to the aromatic nucleus, a factor which seems greatly to enhance activity in the isomeric series, as mentioned above. Compounds of the formula (I; R = *cyclo*alkyl) have not so far been reported, probably owing to the difficulty of synthesising the requisite resorcinols.



(V.)



(VI.)



(VII.)

In efforts to prepare 4-*sec.*-alkylresorcinols by direct alkylation of resorcinol, a variety of conditions was tried. No more than a trace of simple alkylation could be achieved with *n*-octyl alcohol by use of sulphuric acid (cf. Meyer and Bernhauer, *Monatsh.*, 1929, **53/54**, 721), anhydrous hydrogen fluoride (cf. Calcott, Tinker, and Weinmayr, *J. Amer. Chem. Soc.*, 1939, **61**, 1010), or boron fluoride alone (cf. Sowa, Hennion, and Nieuwland, *ibid.*, 1935, **57**, 709) or with the addition of phosphoric oxide (cf. Toussaint and Hennion, *ibid.*, 1940, **62**, 1145). Evidently, for the primary alcohol to effect nuclear alkylation, conditions are required which cause complex decomposition and polymerisation of the resorcinol. *sec.*-Octyl alcohol with anhydrous aluminium chloride and oct-1-ene with fluoboric acid both gave *ca.* 30—40% yields of octylresorcinol. Oct-1-ene with aluminium chloride failed to alkylate resorcinol, apparently becoming itself polymerised. The octylresorcinols from *sec.*-octyl alcohol and oct-1-ene gave rise to the same crystalline *cyclo*hexenocoumarin on treatment with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate and phosphorus oxychloride, in rather small yield in both cases. The coumarin isolated seems to be a *sec.*-octyl compound, and is probably the *1-methylheptyl* compound since it was obtained from oct-1-ene which ought to yield exclusively this isomer (cf. Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," New York, 1941, pp. 461, 466). Treatment with methylmagnesium iodide in the usual manner gave the *tetrahydrodibenzopyran* of probable structure (VII; R = *n*-C_6H_{13}·CHMe).

The five new tetrahydrodibenzopyrans of series (VII) were investigated pharmacologically together with tetrahydrocannabinol, its acetate, and some of its homologues previously described. The Gayer test (cf. Marx and Eckhardt, *Arch. Exp. Path. Pharm.*, 1933, **170**, 395) for corneal areflexia was performed on rabbits, the substances being injected intravenously in solution in propylene glycol. Concentrations were such that the dose to be given per kg. of body weight was always contained in 0·1 ml. Two animals were used for each dose level and the " score " or number of blinks in response to twenty applications of the horse hair to the cornea was determined for each rabbit at intervals after injection. The minimum scores obtained were plotted against the logarithm of the dose in mg. per kg. of body weight, and the relation found to be linear over most of the range. In the results summarised in the table, the activities of the compounds are expressed by the dose reducing the response to the test to 50%, as read from the dosage–response curve. Acute toxicities were determined in mice, also by intravenous injection in propylene glycol solution. A method similar to that described by Davies, Raventos, and Walpole (*Brit. J. Pharmacol.*, 1946, **1**, 255), who reported low activity with cannabis resin extract, was used to investigate analgesic properties. It was found that similar activity is possessed by synthetic tetrahydrocannabinol, higher members of this series, and the only compound (VII; R = *n*-C_6H_{13}) so far tested in the new series. The substances were injected into groups of young rats by subcutaneous route in propylene glycol solution and tested in comparison with parallel groups of rats receiving pethidine hydrochloride, 7·5 mg. per kg. of body weight in aqueous solution. The results given in the table are obtained from the dosage–response curves, which are parallel to that obtained for pethidine hydrochloride.

Reviewing the results in the table, it can be seen that, in spite of differences of structure, the same order of hashish activity in rabbits, analgesic activity in rats, and toxicity in mice exists in the new series (VII) as in the tetrahydrocannabinol series (I). However, it is interesting to observe that the variation of activity with variations in structure of the side

	R =	Gayer test, ED_{50}, mg./kg.	Mice, LD_{50}, mg./kg.	Dose having standard analgesic effect, mg./kg.
Series (I) :	*n*-C_5H_{11} (acetate)	0·3	non-lethal at 200	60·0 (free phenol)
	n-C_6H_{13} (" Synhexyl ")	0·03	140	100·0
	iso-C_6H_{13}	0·3	—	—
	n-C_7H_{15}	0·03	—	—
	sec.-C_8H_{17}	0·0025	390	160·0
Series (VII) :	*n*-C_6H_{13}	0·125	490	50·0
	n-C_7H_{15}	0·06	188	—
	n-C_8H_{17}	0·04	ca. 400	—
	*cyclo*Hexyl	0·04	60	—
	sec.-C_8H_{17}	0·07	ca. 400	—

chain R differs markedly in the two series. We have not yet obtained any new compound with the exceptionally high activity we report for the *sec.*-octyl homologue of (I), which confirms the result published by Adams and Loewe (*loc. cit.*) for this and similar compounds using the dog-ataxia test. It should be pointed out that the tests using rabbits and dogs measure only two aspects of the pharmacology of these substances. So far there is no evidence that the most interesting action of *Cannabis Indica* and its synthetic analogues, its powerful euphoriant effect in man, has any relationship to the ataxia or corneal anæsthesia produced in animals.

The present paper is a continuation of work started in this field by Bergel, Todd, *et al.* (cf. *Annalen*, 1930, **482**, 55; 1932, **493**, 250; *Biochem. J.*, 1939, **33**, 123, etc.).

Experimental.

7-Hydroxy-5'-methyl-6-n-hexyl-3 : 4-cyclohexenocoumarin (V; R = *n*-C_6H_{13}).—4-*n*-Hexylresorcinol (22·0 g.), prepared by Clemmensen reduction of 4-*n*-hexoylresorcinol (Dohme, Cox, and Miller, *J. Amer. Chem. Soc.*, 1926, **48**, 1688), was dissolved in ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (22·0 g.), and concentrated sulphuric acid (40 ml.) added slowly. After standing at room temperature for 21 hours, the dark, viscous reaction mixture was poured on ice with vigorous stirring. The resulting light-brown solid was collected and crystallised from methanol. The *coumarin* consisted of cream-coloured prisms, m. p. 167—168° (Found : C, 75·8; H, 8·2. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%), and exhibited an intense blue fluorescence in solution in alcoholic potassium hydroxide. No colouration was obtained with 2 : 6-dichloroquinonechloroimide (Gibbs, *J. Biol. Chem.*, 1927, **72**, 649).

7-Hydroxy-5'-methyl-6-n-hexyl-3 : 4-benzocoumarin (VI).—(*A*) The above compound (1·0 g.) was intimately mixed with 5% palladised charcoal (0·5 g.) and heated slowly to 260°, evolution of hydrogen then setting in briskly. The temperature was slowly increased to 300—310° and held there until no more hydrogen was given off. The cooled residue was washed with hot alcohol and filtered whilst hot. On cooling, the *benzocoumarin* crystallised in colourless needles, m. p. 220—222°. Recrystallisation did not increase the m. p. (Found : C, 77·2; H, 7·0. $C_{20}H_{22}O_3$ requires C, 77·4; H, 7·15%).

(*B*) 2-Bromo-4-methylbenzoic acid (1·75 g.) and 4-*n*-hexylresorcinol (1·5 g.) were dissolved in N-aqueous sodium hydroxide (10 ml.). The solution was heated to boiling and 10% copper sulphate solution (0·5 ml.) was added, resulting in formation of a brown precipitate which was collected. This became nearly white on washing with alcohol, and on recrystallisation from the same solvent, colourless needles were obtained, m. p. 220—222°. No depression in melting point was observed when the products from procedures (*A*) and (*B*) were mixed.

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-n-hexyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *n*-C_6H_{13}).—The above-described methyl*cyclo*hexeno-coumarin (10·0 g.), dissolved in dry benzene (150 ml.), was added to the Grignard reagent prepared in the usual way from methyl iodide (47·5 g.) and magnesium (8·0 g.) in dry ether (120 ml.). The mixture was boiled under reflux for 15 hours, cooled, and poured on ice. After treatment with saturated ammonium chloride solution, the ether was separated and washed twice with water. Drying, concentration, and distillation of the residue in a vacuum gave the required *tetrahydrodibenzopyran* as a light-amber resin distilling at 180—185°/0·3 mm. (Found : C, 79·9; H, 9·6. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

7-Hydroxy-5'-methyl-6-n-heptyl-3 : 4-cyclohexenocoumarin (V; R = *n*-C_7H_{15}).—4-*n*-Heptylresorcinol (14·5 g.) from 4-*n*-heptoylresorcinol (Dohme, Cox, and Miller, *loc. cit.*) and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (12·8 g.) were dissolved in dry benzene (80 ml.). The solution was boiled for 5 minutes and kept at room temperature for 18 hours. When the dark solution was washed with aqueous sodium hydrogen carbonate, crystallisation began. The pink solid was filtered off, washed with water and benzene, and had m. p. 158—160°. When prepared by the sulphuric acid method, the crystals were pale green. Recrystallisation from 90% alcohol gave the *coumarin* as plates, m. p. 160—161° (Found : C, 76·1; H, 8·6. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-n-heptyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *n*-C_7H_{15}).—The above coumarin was treated with excess of methylmagnesium iodide in ether–benzene in the same manner as for the corresponding hexyl compound. The *dibenzopyran* was an amber resin, b. p. 198—202°/0·2 mm. (Found : C, 80·3; H, 9·6. $C_{23}H_{34}O_2$ requires C, 80·7; H, 10·0%).

7-Hydroxy-5'-methyl-6-n-octyl-3 : 4-cyclohexenocoumarin (V; R = *n*-C_8H_{17}).—4-*n*-Octylresorcinol (Dohme, Cox, and Miller, *loc. cit.*) was treated exactly as the *n*-heptyl compound to give the *coumarin* as pale pink crystals from benzene, m. p. 152—153° (Found : C, 76·7; H, 8·5. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·6%).

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-n-octyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *n*-C_8H_{17}).—Treatment of the above compound with methylmagnesium iodide in the manner already described gave rise to the desired *dibenzopyran* as an amber resin distilling at 193—196°/*ca.* 0·001 mm. (Found: C, 80·0; H, 10·5. $C_{34}H_{56}O_3$ requires C, 80·9; H, 10·2%).

4-cyclo*Hexylresorcinol*.—The method described by Bartlett and Garland (*J. Amer. Chem. Soc.*, 1927, **49**, 2098) was considerably improved by the use of anhydrous hydrogen fluoride as condensing agent. Anhydrous hydrogen fluoride (*ca.* 100 ml.) was run from a cooled, inverted cylinder into a copper vessel with a lid having a thermometer well, stainless-steel stirrer, and hole for making additions (cf. Calcott, Tinker, and Weinmayr, *loc. cit.*) with efficient ice-cooling. Rubber gloves were worn throughout and a good fume-cupboard was employed. Resorcinol (55 g., "AnalaR" grade) was added rapidly with stirring and then *cyclo*hexanol (50 g.) was run in slowly, the temperature being kept below 8°. The mixture was left overnight and then poured on crushed ice in a Pyrex beaker (1 l.). The resulting gummy mass was dissolved in ether and the ethereal solution separated, and washed three times with water and once with sodium hydrogen carbonate solution. The extract was then dried and concentrated to give a gum which was induced to crystallise by trituration with benzene and light petroleum (b. p. 60—80°). The 4-*cyclo*hexylresorcinol was obtained as colourless crystals, m. p. 123—125°. The analytical specimen (recrystallised from benzene and light petroleum) had m. p. 127—128° (Found: C, 74·7; H, 8·2; active H, 1·9 atoms/mol. Calc. for $C_{12}H_{16}O_2$: C, 75·0; H, 8·4%; active H, 2·0 atoms/mol.).

7-Hydroxy-5'-methyl-6-cyclo*hexyl-3* : 4-cyclo*hexenocoumarin* (V; R = *cyclo*hexyl) was prepared by the phosphorus oxychloride method from 4-*cyclo*hexylresorcinol. The substance could not be recrystallised owing to its insolubility but became nearly white when washed with methanol. It had m. p. 280—285° (Found: C, 77·2; H, 7·7. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·75%).

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-cyclo*hexyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran* (VII; R = *cyclo*hexyl).—Reaction of the above coumarin with excess of methylmagnesium iodide yielded the *tetrahydrodibenzopyran* as a light yellow, brittle glass, b. p. 185—195°/*ca.* 0·0006 mm. (Found: C, 80·35; H, 9·0. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·3%).

4-sec.-*Octylresorcinol*.—(*A*) Anhydrous aluminium chloride (66·8 g.) was dissolved in nitrobenzene (130 ml.), and the solution added slowly and with stirring to a mixture of resorcinol (27·5 g.) and *sec.*-octyl alcohol (32·5 g.) dissolved in nitrobenzene (100 ml.), the temperature being kept at 70—80°. Evolution of hydrogen chloride began after about half the aluminium chloride had been added. The mixture was kept at *ca.* 80° for 5 hours and then cooled and poured on ice and hydrochloric acid. Ether was added, and after being separated, the ethereal extract was washed twice with water, dried, and concentrated. The 4-sec.-*octylresorcinol* was obtained as a golden syrup by distillation and collection of the fraction (14·7 g.), b. p. 147—153°/0·1 mm. (Found: C, 75·5; H, 9·9; active H, 2·0 atoms/mol. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0; active H, 2 atoms/mol.).

(*B*) Oct-1-ene (25·0 g.), prepared from the action of *n*-amylmagnesium bromide and allyl chloride or bromide according to Kazanskii *et al.*, (*J. Gen. Chem. U.S.S.R.*, 1947, **17**, 1503; *Chem. Abs.*, 1948, **42**, 2225), was mixed with resorcinol (24·6 g.) and fluoboric acid (1·2 g.) (prepared according to Nieuwland and Sowa, *J. Amer. Chem. Soc.*, 1935, **57**, 454) was added. The mixture was well stirred and heated by means of an oil-bath to 140°. The red liquid obtained was kept at this temperature for 3 hours and then cooled to about 80°, and hot water (80 ml.) added. The aqueous layer was removed, and the residue washed twice more with hot water to remove unchanged resorcinol. On distillation, the *sec.*-octylresorcinol (18·7 g.) was collected at 149—155°/0·1 mm.

7-Hydroxy-5'-methyl-6-sec.-octyl-3 : 4-cyclo*hexenocoumarin* (V; R = *sec.*-C_8H_{17}).—4-*sec.*-Octylresorcinol (12·5 g.) and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate were dissolved in dry benzene (80 ml.) and treated with phosphorus oxychloride (8·65 g.) in the manner already described. When washed, the benzene solution deposited no crystals and concentration led to a red syrup. This was induced to crystallise on treatment with light petroleum (b. p. 80—100°) to give pale pink crystals (4·4 g.), m. p. 192—195°. Recrystallisation from benzene–light petroleum gave the *coumarin* as almost colourless crystals, m. p. 197° (Found: C, 77·4; H, 8·7. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%). This product was the same whether the octylresorcinol from (*A*) or (*B*) was employed.

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-sec.-octyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *sec.*-C_8H_{17}) was obtained from the above coumarin and methylmagnesium iodide as an amber resin, b. p. *ca.* 163°/0·001 mm. (Found: C, 79·9; H, 9·7. $C_{34}H_{56}O_3$ requires C, 80·9; H, 10·2%).

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205. *Curare Alkaloids. Part IX. Examination of Some* Strychnos *Species from British Guiana: Characterisation of Diaboline, an Alkaloid from* Strychnos diaboli, *Sandwith.*

By HAROLD KING.

The aim of this investigation was the survey of the *Strychnos* species of British Guiana, so far as they were accessible, in order to determine which contained alkaloids showing curare activity, in the hope that bases of use in medicine might be found. It has been established that several species contain alkaloids which exhibit curare activity, the most important being *S. toxifera*.

S. diaboli yields a base diaboline which has been characterised.

In 1931 Hartridge and West (*Brain*, **54**, 312) described a rigidity-removing ("lissive") action of curare in experimental parathyroid tetany in dogs. This "lissive" effect was not observed with all samples of curare, and an explanation of the effect in terms of chemical constituents was not possible in view of the backward state of our knowledge of the alkaloids which contribute their effects to the various curares. During the past decade and a half considerable clarification has taken place; for instance, it is now known that the curares prepared by the natives of the northern part of South America come mainly from bush-ropes of the genus *Chondrodendron* or of the genus *Strychnos* or of both.

As a result of an approach made by Dr. Ranyard West to the Medical Research Council in 1931, a broad survey of the curare field was undertaken, and the present communication records the results which have been obtained on certain *Strychnos* species which grow in the Crown Colony of British Guiana. Specimens of the bark, sometimes of the stems, the leaves and in some cases of the flowers have been obtained through the kind co-operation of the Curator of Forests of British Guiana, and the identification of the species has been made finally by Mr. N. Y. Sandwith, M.A., of the Herbarium, Kew. The bark has been examined for alkaloidal content, and the alkaloidal extract tested for curare activity.

Sandwith, in the "Bulletin of Miscellaneous Information," No. 8, for 1933, issued by the Royal Botanic Gardens, Kew, describes nine species of *Strychnos* which occur in British Guiana, for three of which there is very good evidence supplied by reliable explorers and botanists that they have been utilised in the preparation of curare. More recently Krukoff and Monachino (*Brittonia*, 1942, **4**, 248) in a survey of American species of *Strychnos* mention eleven species as occurring in British Guiana, most of which have been recorded at some time or other as furnishing poisons of varying intensity.

The results of the examination of six of these species, and of some others about the identity of which there is some doubt, are recorded below.

Species.	Forest department no.	Alkaloid content.	Curare action.
Strychnos Erichsonii	2284	+++	None
,, *Melinoniana*	2279; 2286; 2303	+	,,
,, *Mitscherlichii*	2261	−	,,
,, ,,	2621	++	Weak
,, *diaboli*	2270	−	None
,, ,,	2295; 2468; 2473	+ to ++	,,
,, *toxifera*	2285; 2278	++	Strong
,, ,,	fruit	−	—
,, *guianensis*	4431	++	Weak
,, near *guianensis*	2467 (*a*)	−	None
,, ,, ,,	2620 (*b*)	++	Active
,, ,, *hirsuta*	2482	++	,,

(*a*, *b*) These are near *S. guianensis* but different from it and are not con-specific. (*b*) may be *S. glabra*, but in the absence of flowers exact identification was impossible.

Two of the species recorded by Richard Schomburgk ("Travels in British Guiana, 1840—1844") as entering into the curare of the Macusi Indians, namely *S. cogens* and *pedunculata*, have not been examined. They grow in a region infrequently visited.

All except one of the *Strychnos* species contain alkaloids, and four of them contain alkaloids with a curare-action. Of the four, *S. toxifera*, which Robert, brother of Richard, Schomburgk regarded as furnishing the main active ingredients of the curare of the Macusi Indians, gave the strongest curare preparations.

As there is considerable evidence that the Indians put the extracts of more than one plant into their curare preparations and even mix extracts from *Chondrodendron* species with those from *Strychnos* species, both of which furnish quaternary alkaloids with a curare-action, it is evident that the safest scientific approach to the problem of the origin and nature of the active principles of curare is by an examination of single, botanically identified *Strychnos* and *Chondrodendron* species.

Hitherto the only South American *Strychnos* species which has received more than a superficial chemical examination has been *S. toxifera* and that by Wieland and his pupils on material supplied by the Medical Research Council. The writer's own investigations were interrupted by the war.

Of the other species recorded in the table, *S. Erichsonii* is very rich in alkaloids, but they seem to resinify with great ease and may need a special technique for their characterisation.

S. diaboli yields a crystalline water-soluble alkaloid *diaboline* with the formula $C_{21}H_{26}O_3N_2$. It is a non-phenolic mono-acidic base containing a methylenedioxy-group (Gaebel's test). It

is doubtful whether an acylatable group is present; certainly no crystalline acyl derivative has been obtained, and nitrous acid gives a crystalline nitrite. The results obtained on methylation are of interest. When the base is boiled in methyl-alcoholic solution with methyl iodide it is converted partly into O-*methyldiaboline methiodide I* and if to the methyl-alcoholic mother liquor potassium hydroxide is added and the boiling continued with more methyl iodide, a second very soluble methiodide is formed which separates, when the solvent is changed to water, as an addition *compound* of potassium iodide and two molecules of *O*-methyldiaboline methiodide II. This additive product is much less soluble in *iso*propyl alcohol and crystallises therefrom in plates. If, however, it is repeatedly crystallised from water it may separate from concentrated solutions as O-*methyldiaboline methiodide II* free from potassium iodide and crystallising in large hemispherical masses.

It is tentatively suggested that the two methiodides, which differ considerably in optical rotation, may contain asymmetric nitrogen analogous to the metho-salts of canadine (Pyman, *J.*, 1913, **103**, 290), and that the third oxygen atom of diaboline is present as a non-phenolic carbinol group in propinquity to one of the nitrogen atoms.

Diaboline has little pharmacological activity. According to Dr. W. D. M. Paton of this Institute, *O*-methyldiaboline methiodide I has a curare-potency on the rabbit head-drop test one fifty-fourth that of *dextro*tubocurarine chloride, whilst that of the isomeric methiodide II is one seventy-ninth that of *dextro*tubocurarine chloride.

I am indebted to Dr. H. S. Forrest for determining the ultra-violet absorption spectrum of diaboline hydrochloride in water. It showed a maximum at 2490 A. in 0·0033% solution. It may be significant that this maximum is also shown by certain members of the calabash alkaloids described by Schmid and Karrer (*Helv. Chim. Acta*, 1947, **30**, 1167 and 2085). As these latter bases also orginate from South American *Strychnos* species, a common ultra-violet chromophore may be indicated. Apart from the striking colour reactions of the calabash alkaloids with the Otto–Wieland reagent there is no evidence of a close structural affinity between the alkaloids of *S. Nux Vomica* and the South American *Strychnos* species.

Experimental.

Preparation of Bark Extracts for Alkaloidal and Physiological Tests.—A known weight of finely powdered bark was slowly percolated with 1% aqueous tartaric acid until the extract no longer gave a reaction with Tanret's reagent or until the extract was very pale. The reaction of Tanret's reagent with a portion of the total percolate gave an indication of alkaloidal content. The test for curare activity was carried out on a neutralised portion of the solution, using the righting reflex in the frog as previously defined (King, *J.*, 1937, 1478), and I am indebted to Professor J. H. Gaddum, F. R. S., and Dr. G. L. Brown, F.R.S., for the physiological results.

When curare activity was found on the crude extract the solution was further purified by addition of basic lead acetate solution so long as a precipitate was formed. Lead ions were then removed from the filtrate and washings with hydrogen sulphide, and the solution prepared for the frog test by removing excess of hydrogen sulphide and final neutralisation. The cleaner solution usually gave a clearer physiological response.

Examination of S. Diaboli *Bark. Isolation of Diaboline.*—Finely powdered bark of *S. diaboli* (55·5 kg.) was percolated with 1% aqueous tartaric acid until the percolate gave only a faint turbidity with Tanret's reagent. The combined percolates were concentrated under reduced pressure at 50° to 22 l., and filtered from calcium and potassium tartrates. A portion (100 c.c.) was treated with aqueous 50% sodium hydroxide (25 c.c.), which kept a phenolic resin in solution, and then extracted 6 times with chloroform. On removal of this solvent the residual alkaloidal gum amounted to 1·55 g., corresponding to a crude alkaloidal content of 0·6% in the bark. Other batches of bark have given alkaloidal contents between 0·2 and 0·5%. The total crude base (199 g.) so obtained was neutralised to litmus with 3N-hydrochloric acid, and the solution extracted with chloroform to remove fat and some colouring matter. It was then concentrated to a syrup which, on keeping, slowly deposited *diaboline hydrochloride* as a very soluble salt which was then crystallised first from water and then from 7 parts of boiling absolute alcohol and then finally from water. By working up the mother liquors about 70 g. of pure salt were obtained.

Diaboline hydrochloride crystallises as a felt of needles which shrink and turn brown near 260° and have no definite m. p. It usually crystallises as a monohydrate, sometimes as a hemihydrate (Found on air-dry solid: loss at 110°, 4·7. $C_{21}H_{26}O_3N_2,HCl,H_2O$ requires H_2O, 4·8%. On dried solid: C, 64·4; H, 6·9; N, 7·2; Cl, 8·9. $C_{21}H_{26}O_3N_2,HCl$ requires C, 64·5; H, 7·0; N, 7·2; Cl, 9·1%). When diaboline is submitted to a Herzig–Meyer process for the determination of *N*-methyl groups it shows the absence of a methoxyl group, but at 270—310° it may yield methyl iodide corresponding to as much as 0·2 of an *N*-methyl group which may arise from partial reduction of methylene di-iodide. The anhydrous salt showed $[\alpha]_{5461}^{20°}$ + 184° in water (*c*, 0·57), whence $[\alpha]_{5461}^{20°}$ + 202·7° for the ion.

The *base* was extracted with chloroform from a strongly alkaline solution of the hydrochloride, and the gum left on removing the chloroform was boiled with ether. It gradually crystallised in silky needles, m. p. 187° (Found: C, 71·1; H, 6·8; N, 8·2. $C_{21}H_{26}O_3N_2$ requires C, 71·1; H, 7·4; N, 7·9%).

The *nitrate* was obtained as a white chalky crystalline powder by exact neutralization of the base with N-nitric acid. It was soluble in 8 parts of hot water and separated in clusters of prisms, m. p. 244° (decomp.) (Found: C, 60·3; H, 6·0; N, 9·6. $C_{21}H_{26}O_3N_2,HNO_3$ requires C, 60·4; 6·5; N, 10·1%);

$[\alpha]_{5461}^{20°}$ + 170·7° in water (*c*, 0·44), whence $[\alpha]_{5461}^{20°}$ + 200·5° for the ion, in close agreement with the value found using the hydrochloride.

The *hydrogen oxalate* crystallises from water in minute tablets, also in rods. When air-dried it melts partly near 100°, and when dried at 97° it has no definite m. p. but swells up between 170° and 180° (Found on air-dry solid: loss at 100° in a vacuum, 9·3. $C_{21}H_{26}O_3N_2,C_2H_2O_4,2{\cdot}5H_2O$ requires H_2O, 9·2%. On dried solid: C, 62·0; H, 6·3; N, 6·4. $C_{21}H_{26}O_3N_2,C_2H_2O_4$ requires C, 62·1; H, 6·4; N, 6·3%).

The *picrate* was obtained from the base (0·12 g.) and picric acid (0·08 g.) in boiling water (100 c.c.). It separated in irregular shaped plates or leaflets which required 440 parts of boiling water for re-solution; m. p. 180—180° (efferv.). Great difficulty was experienced in the analysis of this substance. Although it suffers no loss in weight at 100°, most analyses by different micro-analysts agree with the presence of half a molecule of water (Found: C, 54·5; H, 5·1; N, 11·6. $C_{21}H_{26}O_3N_2,C_6H_3O_7N_3,0{\cdot}5H_2O$ requires C, 54·7; H, 5·1; N, 11·8%). On one occasion a picrate, small rectangular plates, m. p. 242° (decomp.), was obtained from a similar aqueous preparation, but this could never be repeated. It was found, however, that when the low-melting picrate was boiled with absolute alcohol it dissolved and then suddenly separated from the boiling solution in irregular plates, m. p. 244° (decomp.) (Found: C, 56·0; H, 4·7; N, 11·8, 12·4. $C_{21}H_{26}O_3N_2,C_6H_3O_7N_3$ requires C, 55·5; H, 5·0; N, 12·0%). This higher-melting picrate will not dissolve in boiling acetone or methyl ethyl ketone, but will do so if a trace of water is added. It is also very sparingly soluble in boiling ethyl or butyl alcohol.

Methylation of Diaboline.—The base, regenerated from diaboline hydrochloride (28·0 g., $[\alpha]_{5461}$ + 186°), was dissolved in methyl alcohol (150 c.c.) and methyl iodide (20 c.c.). After the solution had been boiled gently for 3 hours, one half of the solvent was distilled off, and on keeping a felt of prisms separated of crude methiodide I (13·8 g.), m. p. 282° (decomp.). The methyl-alcoholic filtrate was treated with methyl iodide (15 c.c.) and a solution of potassium hydroxide (7 g.) in methyl alcohol (40 c.c.) and boiled gently for an hour. The solution was then distilled to remove methyl alcohol, water being added in small portions to dissolve potassium iodide as it separated. Finally, crude methiodide II separated (16·1 g.), m. p. 232°. On careful fractionation of the mother liquors further crops of each methiodide were obtained.

A portion of crude methiodide I was crystallised from 4 volumes of hot water and then separated in prisms, m. p. 290° (decomp.) (Found: loss at 100°, 8·2. $C_{23}H_{31}O_3N_2I,2{\cdot}5H_2O$ requires H_2O, 8·1%. On substance dried at 100°: C, 53·8; H, 5·6; I, 24·9; OMe, 6·0; NMe, 5·9. $C_{23}H_{31}O_3N_2I$ requires C, 54·1; H, 6·1; I, 24·9; OMe, 6·1; NMe, 5·7%). Analysis shows that this substance is *O-methyldiaboline methiodide I*. The anhydrous salt showed $[\alpha]_D^{20°}$ + 43·5° in water (*c*, 0·68). This gave a *picrate* crystallising from water in needles, m. p. 150—160°, which when recrystallised from methyl alcohol separated in thin leaflets, m. p. 213—214° (Found: C, 56·9; H, 5·2; N, 11·8. $C_{29}H_{33}O_{10}N_5$ requires C, 56·9; H, 5·4; N, 11·5%).

If crude methiodide II is crystallised from 20 volumes of *iso*propyl alcohol it separates in bold prisms, m. p. 235—238°, which consist of an *addition compound* of *O*-methyldiaboline methiodide II and half a molecule of potassium iodide [Found: loss at 100°, 4·0. $(C_{23}H_{31}O_3N_2I)_2,KI,1{\cdot}5H_2O$ requires H_2O, 4·3%. On anhydrous salt: C, 47·0; H, 5·2; N, 5·1; I, 31·6. $(C_{23}H_{31}O_3N_2I)_2,KI$ requires C, 46·5; H, 5·3; N, 4·7; I, 32·0%]. On ignition with sulphuric acid it left a residue of potassium sulphate.

If the crude methiodide II is crystallised from less than its own weight of water many times, it may lose the potassium iodide and then separates from water in large hemispherical masses built up compactly of prisms. *O-Methyldiaboline methiodide II* so obtained melts below 100° but when dried at 90° melts between 200° and 220° (Found: C, 48·9; H, 6·7; N, 5·3; I, 22·6; H_2O, 8·1, OMe, 5·9; NMe, 4·9. $C_{23}H_{31}O_3N_2I,2{\cdot}5H_2O$ requires C, 49·2; H, 6·5; N, 5·1; I, 22·9; H_2O, 8·1; OMe, 5·6; NMe, 5·2%). Unlike the addition compound with potassium iodide this salt is readily soluble in *iso*propyl alcohol. It is also soluble in acetone and in chloroform. The anhydrous salt showed $[\alpha]_D^{20°}$ + 143·9° in water (c, 0·73). The picrate is amorphous, but a perchlorate is readily obtained, crystallising in diamond-shaped plates.

If *O*-methyldiaboline methiodide I is boiled for 3·5 hours with methyl-alcoholic potash (5% solution) and then for an additional 1·5 hours with excess of methyl iodide, the original methiodide I is recovered unchanged. If diaboline is boiled with methyl iodide and methyl-alcoholic potash, both methiodides I and II are formed.

The strongly alkaline aqueous solutions from which the chloroform-soluble bases, mainly diaboline, had been removed were neutralized and precipitated with mercuric chloride. The quaternary fraction freed from mercury ions was only obtained in the amorphous state and was devoid of noticeable pharmacological action.

I am indebted to my assistant Mr. E. V. Wright for considerable help with the extraction of the barks.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH,
HAMPSTEAD, N.W.3.

[*Received, September 22nd*, 1948.]

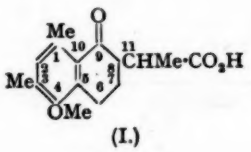
206. *The Constitution of ψ-Santonin. Part V. Further Studies of the Chemistry of Desmotropo-ψ-santonin.*

By Wesley Cocker, B. E. Cross, and Cyril Lipman.

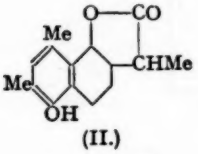
It has been shown that desmotropo-ψ-santonin is a saturated lactone best represented by structure (II) (compare Clemo and Cocker, *J.*, 1946, 30; Cocker and Lipman, *J.*, 1947, 533). The desmotropo-ψ-santonin described by Clemo and Cocker is now named (+)β-desmotropo-ψ-santonin (compare the nomenclature suggested by Huang-Minlon, Lo, and Chu, *J. Amer. Chem. Soc.*, 1943, **65**, 1780, for the desmotropo-santonins).* A second desmotropo-compound (+)α-iso*desmotropo-ψ-santonin* has been isolated from the mother-liquors obtained from the crystallisation of (+)β-desmotropo-ψ-santonin. Two further dextrorotatory desmotropo-compounds, (+)β-iso- and (+)α-*desmotropo-ψ-santonin* have been obtained by heating (+)α-iso- and (+)β-desmotropo-ψ-santonin, respectively, with anhydrous potassium carbonate in anhydrous xylene. All the four possible dextrorotatory desmotropo-ψ-santonins are now known. A mechanism for the conversion of ψ-santonin into its desmotropo-compounds is suggested.

In an earlier paper Cocker and Lipman (*loc. cit.*) suggested that (+)β-desmotropo-ψ-santonin was an unsaturated phenolic lactone. The methyl ether of the corresponding acid was considered to be (I), but comparison with a synthetic compound of this structure was impossible owing to an inability to racemise the former acid.

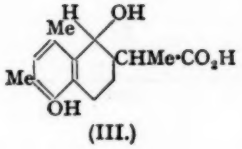
Active-hydrogen determinations on the methyl ether of desmotropo-ψ-santoninic acid (III) gave consistent results indicative of the presence of only one active hydrogen, and could be considered to support the suggestions of Cocker and Lipman. It is, however, possible that a hydroxyl group at C_9 might be undetectable by the Zerewitinoff method, owing to steric hindrance. Efforts made to reach a decision, by chemical methods, on the saturated or unsaturated character of the lactone ring in (+)β-desmotropo-ψ-santonin have been fruitless. This compound was not reduced by catalytic methods, by zinc and hydrochloric acid, or by sodium amalgam, nor could it be oxidised by permanganate, hypobromite, hydrogen peroxide, or potassium *tert.*-butoxide.



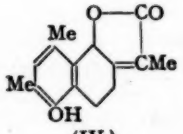
(I.)



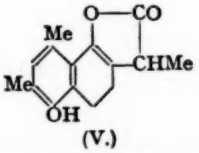
(II.)



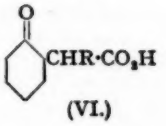
(III.)



(IV.)



(V.)



(VI.)

Failure to oxidise the desmotropo-compound may be parallelled in the santonin series, since so far as we are aware none of the desmotropo-santonins has been oxidised to the corresponding unsaturated lactones or keto-acids. It is probable that, owing to steric hindrance, oxidation at C_9 in compounds of type (II) and (III) is difficult or impossible.

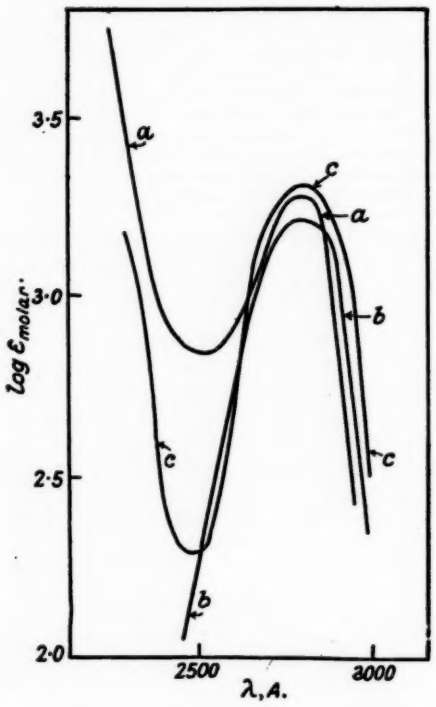
The earlier views of Clemo and Cocker (*loc. cit.*) on the structure of desmotropo-ψ-santonin were eventually confirmed by analysis of a number of different specimens of this compound, its methyl ether, its acetate, its benzoate, and its *carbanilate*.

Spectroscopic evidence lends support to the analytical data. Fig. 1 shows that (+)β-desmotropo-ψ-santonin has a light-absorption curve similar to that of phenol (Wolf and Herold, *Z. physikal. Chem.*, 1931, *B*, **13**, 201) and the saturated acid, γ-(6-methoxy-1 : 2 : 3 : 4-tetrahydro-1-naphthyl)butyric acid (Stork, *J. Amer. Chem. Soc.*, 1947, **69**, 2936). Structures (II) and (III) would be expected to show such light-absorption characteristics. A compound of structure (IV) —an αβ-butenolide—would be expected to absorb like eugenol, whilst its βγ-isomeride (V) would be expected to absorb like *iso*eugenol (Fig. 2). *iso*Eugenol absorbs quite differently from phenol both qualitatively and quantitatively, and although eugenol (Paersch, Diss., Berlin, 1932) is qualitatively like phenol, eugenol shows a higher intensity of absorption at the maximum.

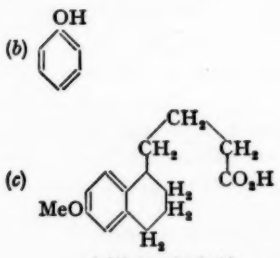
* On this nomenclature the lower-melting isomers are of the α-series, and the higher-melting isomers of the β-series.

Fig. 2 also shows that the lactone of 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-α-propionic acid (Cocker and Lipman, *loc. cit.*) has a light-absorption curve similar to that of eugenol, which agrees with the suggestion made by Cocker and Hornsby (*J.*, 1947, 1157) that keto-acids of the type (VI) cyclise to give αβ-butenolides.

FIG. 1.

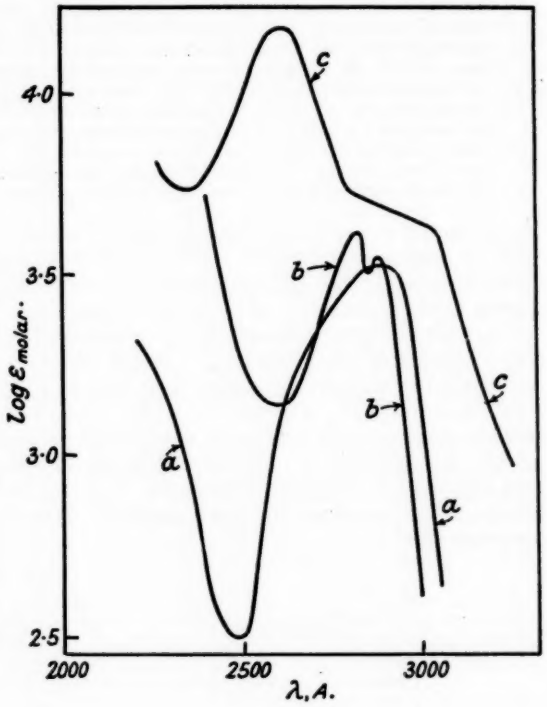


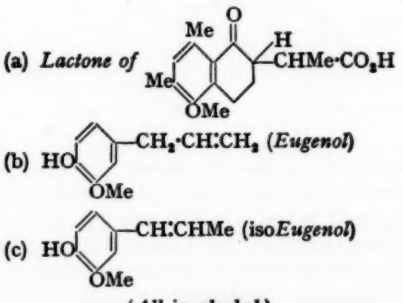
(a) (+) *β-Desmotropo-ψ-santonin.*



(*All in alcohol.*)

FIG. 2.





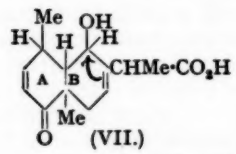
(*All in alcohol.*)

The existence of a saturated lactone ring in (+)β-desmotropo-ψ-santonin is confirmed by the isolation of three other dextrorotatory desmotropo-compounds, which can be represented by structure (II).

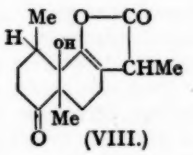
When ψ-santonin is treated with *cold* concentrated hydrochloric acid or 50% sulphuric acid, a dextrorotatory carboxylic acid is produced (Clemo and Cocker, *loc. cit.*) to which we now give the name ψ-santonic acid. The chemistry of this compound will be dealt with in a later communication but the evidence, chemical and spectroscopic, which we possess leads us to suggest the tentative structure (VII). It possesses two double bonds, one of which is conjugated with the keto-group while the other is in the second ring. This acid is an intermediate in the formation of the desmotropo-compounds since on being heated at 50° with 50% sulphuric acid, ψ-santonic acid gives the desmotropo-ψ-santonin (II).

The two structures (VIII) and (IX) have already been advanced for ψ-santonin (see earlier publication in this series) but structure (X) is a further possibility.

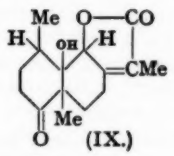
If structure (VII) is correct for ψ-santonic acid, then the formation of this acid from ψ-santonin involves the loss of water from C_1–C_{10} and migration of the double bond so formed to the αβ-position with respect to the keto-group. The second double bond in ψ-santonic acid is probably that associated with the lactone ring in ψ-santonin. The conversion of ψ-santonic acid into desmotropo-ψ-santonin (II) may involve the migration of the double bond of ring B to ring A in the direction shown by the arrow to give a form such as (XI), the angular methyl group of which might be expected to migrate to C_3 with consequent aromatisation of ring A. These changes will have far-reaching stereochemical implications. The asymmetric centres at C_1, C_5, and C_{10} are destroyed and a structure is obtained in which all the centres in the lactone



(VII.)

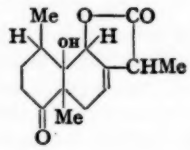


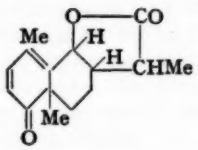
(VIII.)



(IX.)

(X.)





(XI.)

ring are asymmetric. The conversion of structures (VIII) and (X) through (VII) into desmotropo-ψ-santonin would probably lead to a mixture of two pairs of diastereoisomers in both of which the configuration at C_{11} should be the same. This is possible, since it is most unlikely that C_{11} is affected by acid reagents [compare Huang-Minlon *et al.*, *loc. cit.*; *J. Chinese Chem. Soc.*, **1943**, **10**, 126; *J. Amer. Chem. Soc.*, **1948**, **70**, 611, who made the same assumption for the conversion of *l*-santonin into (−)α-desmotroposantonin]. Unless the diastereoisomers form diastereo-compounds or solid solutions, separation into four desmotropo-compounds should be possible. Two of the latter compounds should have the *cis*- and the other two the *trans*-configuration at C_8–C_9.

Experimentally, we find that when ψ-santonin is heated with 55% sulphuric acid a dark red solution is produced from which a mixture of at least two desmotropo-compounds separates. Crystallisation of this mixture from dilute alcohol yields (+)β-desmotropo-ψ-santonin (m. p. 189°, $[\alpha]_D^{15°}$ + 68°), already described, and a second desmotropo-compound, (+)α-iso*desmotropo-ψ-santonin* which after several crystallisations melts at 251—253°, $[\alpha]_D^{20°}$ + 68·5°. The latter compound may not be quite optically pure, since the yields of this material are very small, and it is possible that the specific rotation should be slightly higher. Nevertheless, it is significant that the rotations of the two desmotropo-compounds are almost identical. This may be due to a small optical contribution by one of the centres C_8 or C_9. Another alternative is that the two compounds are pairs of diastereoisomers in solid solution or existing as diastereo-compounds, so that C_{11} is the only optically effective centre, but this is unlikely in view of the transformations to be described below. Finally, (+)β-desmotropo-ψ-santonin and (+)α-*iso*desmotropo-ψ-santonin can only differ in configuration at C_8 or C_9, otherwise (+)α-*desmotropo-ψ-santonin* (below) would be the enantiomorph of (+)α-*iso*desmotropo-ψ-santonin and (+)β-iso*desmotropo-ψ-santonin* would be the enantiomorph of (+)β-desmotropo-ψ-santonin.

On dilution of the red solution from which the two desmotropo-compounds separate, a gum is produced which so far has proved intractable. This gum may contain a mixture of the still unknown lævorotatory compounds, (−)β-*iso*desmotropo-ψ-santonin and (−)α-desmotropo-ψ-santonin.

When (+)β-desmotropo-ψ-santonin is heated with sodium hydroxide at 200°, it yields a small quantity of a further desmotropo-compound, (+)α-*desmotropo-ψ-santonin*, m. p. 171—172°, $[\alpha]_D^{20°}$ + 153°. The same compound is produced in good yield when (+)β-desmotropo-ψ-santonin is heated in boiling xylene with anhydrous potassium carbonate. Under the latter conditions it is likely that C_{11} is inverted, whilst C_8 and C_9 are unaffected (compare Huang-Minlon *et al.*, *loc. cit.*). The lactone ring is not opened in this reaction when the potassium carbonate is perfectly anhydrous, since the inverted lactone can be isolated from the xylene

without the use of mineral acid. The same inverted lactone is obtained even when some of the lactone is hydrolysed. Inversion probably occurs through the enol. Further, all the available evidence (compare Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 689; *Ann. Reports*, 1946, **43**, 165, where references to the work of Kenyon *et al.* are given) goes to show that oxygen–alkyl fission is the exception rather than the rule in the hydrolysis of esters and this mechanism is favoured by ionising conditions which are absent in the experiments described. As the specific rotation is increased by inversion of C_{11}, this centre in (+)β-desmotropo-ψ-santonin and in ψ-santonin itself must be lævorotatory. However, a true assessment of the value of the rotatory power of C_{11} in these compounds cannot be made since vicinal effects from C_8 and C_9 are likely to operate (compare Kauzmann, Walter, and Eyring, *Chem. Reviews*, 1940, **26**, 339).

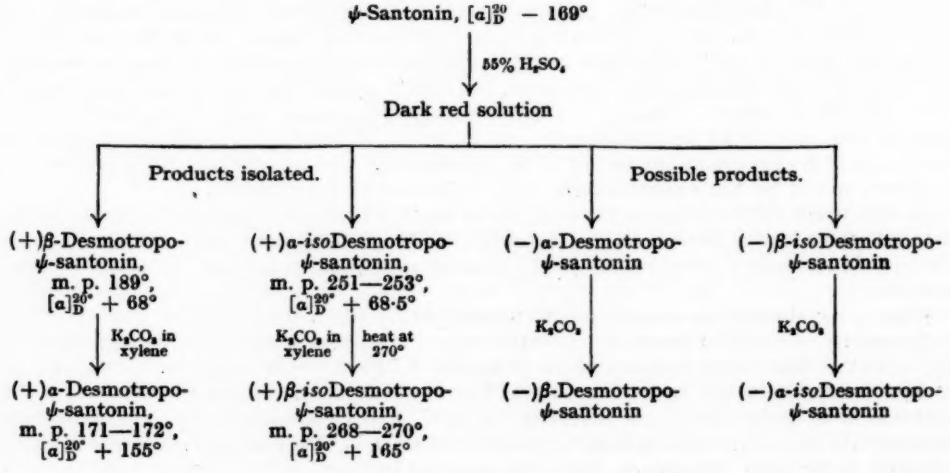
In addition to (+)α-desmotropo-ψ-santonin a further product was isolated (in varying yield) from the alkaline inversion described. After several crystallisations the latter melted at 188—189° ($[\alpha]_D^{20°}$ + 113°). It gave no depression in melting point with a synthetic mixture of equal amounts of (+)α- and (+)β-desmotropo-ψ-santonin, and the specific rotation of this mixture was +113°. This mixture could be crystallised without change in rotation or melting point and, like the product of the inversion described, was probably a solid solution of the two compounds.

By a similar treatment with potassium carbonate in xylene, (+)α-*iso*desmotropo-ψ-santonin is inverted at C_{11} to yield the fourth, and only remaining, possible dextrorotatory desmotropo-ψ-santonin, namely, (+)β-iso*desmotropo-ψ-santonin*, m. p. 268—270°, $[\alpha]_D^{20°}$ + 165°. This compound is also obtained in excellent yield when (+)α-*iso*desmotropo-ψ-santonin is heated above its melting point, although no such inversion takes place on heating either (+)α- or (+)β-desmotropo-ψ-santonin. Inversion of C_{11} most likely takes place by enolisation of the carbonyl group in the lactone ring, a process which need not involve the opening of the lactone ring. As expected, the specific rotation is increased by roughly the same value during the inversion of (+)α-*iso*- and (+)β-desmotropo-ψ-santonin.

The following new derivatives of the above desmotropo-compounds have been prepared : *methyl ether* and *acetate* of (+)α-desmotropo-ψ-santonin, the *acetate* of (+)β-*iso*desmotropo-ψ-santonin, and the *acetate* of (+)α-*iso*desmotropo-ψ-santonin. The specific rotations of these compounds are roughly in agreement with the expected values, indicating the absence of stereochemical changes during acetylation and methylation. The acetate of (+)β-desmotropo-ψ-santonin is the chief product obtained when ψ-santonin is warmed at 50° with acetic anhydride and concentrated sulphuric acid.

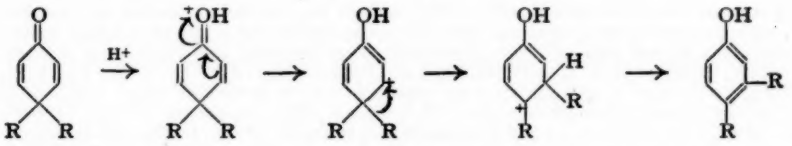
Attempts to produce the lævorotatory desmotropo-compounds by inversion of C_8 and C_9, by acidic reagents, in any of the dextrorotatory desmotropo-compounds described (compare Huang-Minlon *et al.*, *loc. cit.*) have so far failed, but further investigations are in hand. As already stated, two of the lævorotatory desmotropo-compounds may be found in the red solution described, and this is also being investigated. We hope to study the relative stability of the lactone ring in the two series of desmotropo-compounds (normal and *iso*) with a view to arrive at the configurations of C_8 and C_9.

Many of the reactions described are summarised in the accompanying scheme.

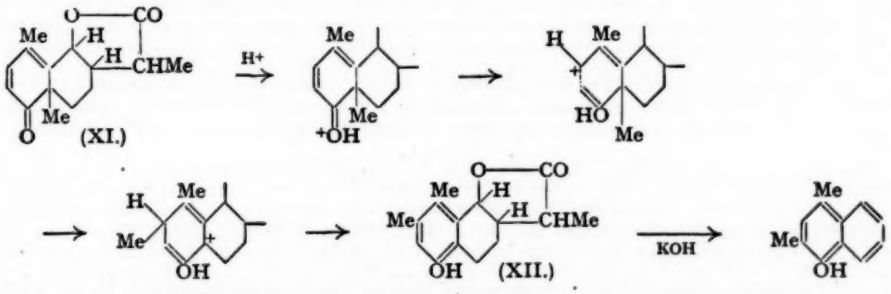


The formation of the desmotropo-compounds from ψ-santonic acid may take place through an unstable intermediate compound such as (XI). This could undergo rearrangement. But the migration of methyl from C_5 to C_3 in such a compound is unusual.

The migration of methyl in semiquinones has been studied by Arnold, Buckley, and Richter (*J. Amer. Chem. Soc.*, 1947, **69**, 2322) who advance the mechanism given below. This mechanism has been used by Huang-Minlon (*J. Amer. Chem. Soc.*, 1948, **70**, 611) to explain the conversion of santonin into desmotropo-santonin (see also Clemo, Haworth, and Walton, *J.*, 1929, 2368, who also give earlier references).

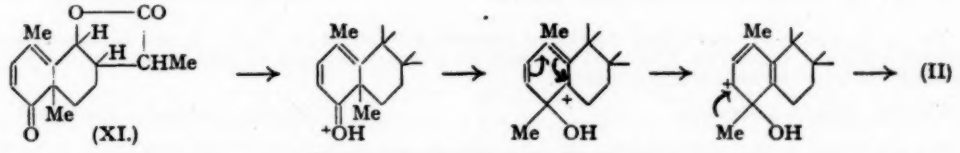


Such a series of changes is not directly applicable to the partial aromatisation of (XI), but it is possible that (XI) could be converted into the form (XII), and that during dehydrogenation, which Clemo and Cocker (*loc. cit.*) effected by fusion of (+)β-desmotropo-ψ-santonin with potash, further migration of the methyl to give 2 : 4-dimethyl-1-naphthol might take place. On this view (XII) would represent desmotropo-ψ-santonin.



In order to test the above hypothesis, 3 : 4-dimethyl-5 : 6 : 7 : 8-tetrahydro-1-naphthol and 3 : 4-dimethyl-1-naphthol * were fused with potassium hydroxide under the conditions employed by Clemo and Cocker. No migration of the methyl group took place and it is now considered that (II) correctly represents desmotropo-ψ-santonin, particularly in view of the fact that this compound fails to couple with diazonium compounds. It may be added that *o*-4-xylenol is also recovered unchanged after fusion with potassium hydroxide.

The production of desmotropo-ψ-santonin from a compound such as (XI) might, however, proceed along the following lines :—



It was stated above that the conversion of ψ-santonic acid into desmotropo-ψ-santonin probably takes place by bond migration. Another, less likely alternative is that the desmotropo-compounds are formed by an oxidation–reduction mechanism in which ring A of ψ-santonic acid is dehydrogenated and the second double bond becomes reduced. The desmotropic change was carried out in presence of benzoquinone as a hydrogen acceptor, but there was no evidence of the production of quinol.

Experimental.

(+)α-iso*Desmotropo-ψ-santonin*.—ψ-Santonin (6 g.) was treated with 50% sulphuric acid as described by Clemo and Cocker (*loc. cit.*). The crude product (1·9 g.) was crystallised (charcoal) from a mixture of alcohol (35 c.c.) and water (12 c.c.), yielding a compound (*A*) (1·3 g.), m. p. 182—186°. The mother-

* The preparation of these compounds from *o*-4-xylenol and succinic anhydride will be described in a separate publication on certain substituted naphthols.

liquor from (*A*) was concentrated, and a second fraction (*B*) (0·4 g.), m. p. 165—230°, was obtained. Crystallisation of (*A*) from dilute alcohol yielded (+)β-desmotropo-ψ-santonin, m. p. 188—189°.

Phenylhydrazide of (+)β-Desmotropo-ψ-santoninic Acid.—A mixture of (+)β-desmotropo-ψ-santonin (0·1 g.) and phenylhydrazine (0·3 g.) was heated at 140—150° for 9 hours. On cooling, the *phenylhydrazide* was collected, washed with a little ice-cold alcohol, and crystallised twice from dilute alcohol, forming colourless needles, m. p. 228—229° (Found: C, 70·6; H, 7·3. $C_{21}H_{26}O_3N_2$ requires C, 71·2; H, 7·3%). Its *methyl ether*, prepared in the same manner from the methyl ether of (+)β-desmotropo-ψ-santonin, crystallised from dilute alcohol in silky needles, m. p. 212—213° (Found: N, 7·4. $C_{22}H_{28}O_3N_2$ requires N, 7·6%).

The mother-liquor from which the (+)β-desmotropo-ψ-santonin separated was mixed with a dilute alcoholic solution of (*B*) (see above) and the mixture was passed through a column of activated alumina, the effluent from which was concentrated. On cooling, this yielded a fraction (about 100 mg.), m. p. 215—230°, rich in (+)α-iso*desmotropo-ψ-santonin*. The combined crops of crystals from several such processes were crystallised several times alternately from benzene and dilute alcohol, yielding needles, m. p. 251—253°, $[\alpha]_D^{20°}$ + 68·5° (*c* 0·71, in alcohol) (Found: C, 72·9; H, 7·45. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Its *acetate* crystallised from absolute alcohol in needles, m. p. 244·5—245·5°, $[\alpha]_D^{20°}$ + 64·1° (*c* 0·4, in chloroform) (Found: C, 70·5; H, 6·95. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%).

(+)α-*Desmotropo-ψ-santonin.*—(+)β-Desmotropo-ψ-santonin (0·5 g.) in anhydrous xylene (10—15 c.c.) was refluxed for 24 hours with freshly ignited potassium carbonate (0·8 g.). The hot mixture was filtered, giving a residue (*A*) and a filtrate (*B*). The latter was evaporated in a vacuum and warmed with concentrated hydrochloric acid, and the *α-desmotropo-ψ-santonin* (0·35 g.), m. p. 164°, was crystallised several times from dilute alcohol and obtained as colourless rosettes of needles, m. p. 171—172°, $[\alpha]_D^{20°}$ + 155° (*c* 0·7, in chloorform) (Found: C, 73·4; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Its *acetate* crystallised from absolute alcohol as needles or prisms, m. p. 214°, $[\alpha]_D^{18°}$ + 121° (*c* 0·55, in chloroform) (Found: C, 71·3; H, 7·2. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%); on deacetylation with alcoholic potash, (+)α-desmotropo-ψ-santonin was recovered. Its *methyl ether* crystallised from dilute alcohol in silvery plates, m. p. 150° (Found: C, 73·5; H, 7·8. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%).

When the residue (*A*) (above) was warmed with concentrated hydrochloric acid, a product (0·1 g.), m. p. 183°, was obtained. Several crystallisations from dilute alcohol yielded colourless rhombs, m. p. 189—190°, $[\alpha]_D^{18°}$ + 113° (*c* 0·9, in chloroform) (Found: C, 73·1; H, 7·5. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). This molecular *compound* depressed the m. p. of (+)β-desmotropo-ψ-santonin, but did not depress the m. p. of the colourless rhombs obtained by crystallising a mixture of equal quantities of (+)α- and (+)β-desmotropo-ψ-santonin from dilute alcohol; this mixture gave $[\alpha]_D^{19°}$ + 112·6° (*c* 0·1, in chloroform).

(+)β-iso*Desmotropo-ψ-santonin.*—A mixture of (+)α-*iso*desmotropo-ψ-santonin (0·21 g.), freshly ignited potassium carbonate (0·63 g.), and anhydrous xylene (25 c.c.) was heated under reflux for 22 hours. The xylene was removed in a vacuum, the residue heated with concentrated hydrochloric acid, and the β-iso*desmotropo-ψ-santonin* collected (0·2 g.), m. p. 245—250°; $[\alpha]_D^{20°}$ + 135·5° (*c* 0·5, in chloroform). It was crystallised several times from absolute alcohol and obtained as slender, colourless needles, m. p. 268—270°, $[\alpha]_D^{18°}$ + 165° (*c* 0·4 in chloroform) (Found: C, 73·1; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). Its *acetate* crystallised from dilute acetic acid in fine, colourless needles, m. p. 223—224°, $[\alpha]_D^{14°}$ + 135° (*c* 0·3, in chloroform) (Found: C, 71·0; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%). (+)β-*iso*Desmotropo-ψ-santonin was also obtained when (+)α-*iso*desmotropo-ψ-santonin (200 mg.) was heated in a sealed tube at 250—270° for 60—70 minutes. The crystalline product, m. p. 256—262°, was recrystallised from absolute alcohol and obtained (90—100 mg.) as colourless needles, m. p. 268—270°, $[\alpha]_D^{18°}$ + 165° (Found: C, 73·6; H, 7·1. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

The *carbanilate* of (+)β-*desmotropo-ψ-santonin* crystallised from alcohol as silvery plates, m. p. 222—223° (Found: C, 71·8, 71·5; H, 6·3, 6·5. $C_{22}H_{23}O_4N$ requires C, 72·3; H, 6·3%).

Acetate of (+)β-Desmotropo-ψ-santonin (compare Clemo and Cocker, *loc. cit.*).—A mixture of ψ-santonin (0·1 g.), acetic anhydride (5·0 g.), and concentrated sulphuric acid (5 g.) was heated at 50° for 20 minutes, cooled, and diluted. The solid product was crystallised twice from alcohol, giving the required acetate, m. p. 230—231° undepressed by authentic acetate.

The authors wish to record their thanks for generous gifts made by Messrs. T. and H. Smith, Ltd., Imperial Chemical Industries, Ltd., and the Medical Research Council of Ireland, and to the Royal Dublin Society for the loan of a polarimeter.

TRINITY COLLEGE, DUBLIN. [*Received, September 22nd,* 1948.]

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207. *The Non-benzenoid Aromatic Hydrocarbon Pentalene. A Theoretical Discussion.*

By D. P. CRAIG and ALLAN MACCOLL.

Pentalene is an unknown hydrocarbon with two fused five-membered rings and four double bonds. Reported attempts to prepare it have failed. A quantum-mechanical study by the valence-bond and the molecular orbital method is given. This shows, on both views, that a considerable resonance energy ought to be associated with the molecule (comparable with benzene). But in the valence-bond method this large resonance energy is developed in a state which lacks the full symmetry of the carbon framework. Bond orders for the molecule are reported in both approximations, and the energies of the lowest triplet and excited singlet states are calculated.

A NUMBER of non-benzenoid aromatic hydrocarbons, such as azulene (I) and *cyclo*octatetraene (II) are now well known (see Baker, *J.*, 1945, 258) but there are still some apparently simple molecules in this class which have not been prepared. This paper will be primarily concerned with pentalene (III), although heptalene (IV) is in some ways similar. *cyclo*Butadiene (V) has been considered by Penney (*Proc. Roy. Soc.*, 1934, **146**, *A*, 233) and recently by Coulson and Moffitt. The latter have shown that its stability is marginal (private communication, and see also *J. Chem. Physics*, 1947, **15**, 151). Both pentalene and heptalene have resisted attempts at preparation. Barrett and Linstead (*J.*, 1936, 612) sought to prepare the former, and Horn, Nunn, and Rapson (*Nature*, 1947, **160**, 830) the latter. Neither attempt was successful. It is striking, too, that no derivatives of these molecules have been reported as occurring naturally, yet those of azulene are well known. Further, the considerations which assist the organic chemist in assessing the chances of preparing a given molecule do not afford any very convincing

(I.) (II.) (III.) (IV.) (V.)

grounds for believing that either pentalene or heptalene should be specially set apart from azulene.

A theoretical study of pentalene is now given. It is found that in the valence-bond approximation, pentalene (and this applies equally to heptalene) has a feature which distinguishes it from azulene, and from the usual six-membered ring hydrocarbons. The difference lies in the symmetry properties of the wave function which describes the ground state of the aromatic (π) electrons: in azulene and all the benzenoid hydrocarbons this wave function has the full symmetry of the carbon " skeleton ", but in pentalene and heptalene this is no longer true and the ground state wave functions show properties of anti-symmetry which in other molecules are associated only with *excited* molecular states. That this should make pentalene and heptalene difficult to prepare must be admitted to be intuitive rather than logical.

The Quantal Treatment.—The quantal treatment of conjugated molecules depends upon the classification of the valency electrons. Carbon in its quadrivalent state has the structure $1s^2 2s 2p^3$. The $2s$, $2p_x$, $2p_y$ orbitals are hybridised to form the so-called trigonal or σ orbitals (see Coulson, *Quart. Reviews*, 1947, **1**, 144), while the $2p_z$ or π orbitals retain their individuality. The σ orbitals are used to form the framework C–C and C–H bonds, and the π orbitals, one for each carbon atom, give the conjugation properties. The usual quantal approximation to conjugated systems treats only the π electrons. Two methods of attack are in common use. In the first, the valence-bond (V.B.) method, account is taken of the fact that the π electrons may be paired in a number of different ways. Each of these ways of pairing corresponds with a structure, no single one being an adequate representation of the state of the molecule. A better representation is given by a combination of the structures, and quantum theory shows how to obtain the combination with the lowest energy. This process of minimising the energy gives rise to the quantum-mechanical secular equation, the roots of which are approximations to the energy levels of the molecule.

In the second method, the method of molecular orbitals (M.O.), the energy levels of a single π electron are found in the combined potential field of the nuclei and of the other electrons. The energy is determined with the use of molecular orbitals formed by linear combination of atomic orbitals, one for each carbon atom. Minimising the energy leads to another secular equation, the roots of which are the energies of the single-electron m.o.s. The electrons are fed, two at a time, into the orbitals of lowest energy, and the molecular energy is found by adding the energies of the occupied orbitals.

Both methods have been much used to calculate the resonance energies of molecules. In each case the resonance energy is the energy difference between the calculated ground state and a hypothetical structure in which the π electrons are localised in specified bonds. In the V.B. method results are obtained in terms of α, the quantum-mechanical exchange integral, and in the M.O. they are obtained in terms of γ, the resonance integral. No attempt is made to compute these integrals: they are evaluated empirically. Wheland (*J. Amer. Chem. Soc.*, 1941, **63**, 2025) has shown that for a large number of molecules the two methods are in agreement, provided γ is set equal to $0{\cdot}55\alpha$. However, Coulson and Rushbrooke (*Proc. Camb. Phil. Soc.*, 1940, **36**, 193) have put forward reasons for supposing that the M.O. method may not be reliable in the case of pentalene, and indeed a discrepancy between the two methods has been noticed by Syrkin and Diatkina (*Acta Physicochim. U.R.S.S.*, 1946, **21**, 641).

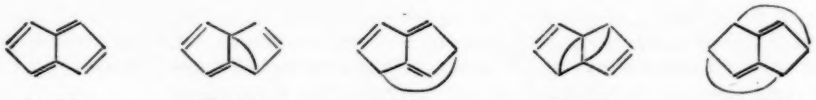
The energy difference between the ground and the first excited molecular level is called the transition energy, and corresponds with the long-wave-length absorption frequency of the molecule. The V.B. method has been very successful in accounting for the light absorption of conjugated systems (Maccoll, *Quart. Reviews*, 1947, **1**, 16); but the M.O. method suffers from the fact that in it the first excited state has both singlet and triplet components, and the separation of these is left out of consideration; consequently, transition energies are not so accurately calculable as in the V.B. treatment.

The methods have been used for a calculation of the bond distances of molecules (Penney, *Proc. Roy. Soc.*, 1937, **158**, *A*, 306; Coulson, *ibid.*, 1939, **169**, *A*, 413). The results are expressed in terms of the bond order, which is empirically related to the bond distance. The agreement between the two methods is good for the majority of molecules.

Most molecules have a singlet ground state, that is, the π electron spins are coupled to give zero resultant spin. In pentalene it seemed possible that the ground state might be a triplet, *i.e.*, that it might have two of its electrons unpaired. The V.B. method, with its explicit account of electron spin, is the more suitable to test this possibility.

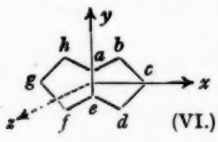
In the present paper the two methods are used to calculate the resonance energy, light absorption, and bond orders for pentalene. In addition, for the reason that has been explained, the V.B. method is used for a calculation of the lowest triplet level.

The Valence-bond Method.—Singlet states. This method starts with a canonical set of structures (Rumer, *Göttingen Nachr.*, 1932, 337), in terms of which any structure may be represented by appropriate linear combination. There are 14 canonical structures for pentalene, two with all " effective " bonds (*A*), eight with one " ineffective " bond (*B* and *C*), and four with two " ineffective " bonds (*D* and *E*). Typical structures are :



A_1 (2). B_1 (4). C_1 (4). D_1 (2). E_1 (2).

The complete secular equation is then of the fourteenth degree. However, symmetry may be used to reduce it to two fifth-degree equations and two quadratics. Pentalene has the symmetry D_{2h}. Each of the structures of the canonical set is associated with a bond eigen-function, and to reduce the secular equation transformation properties of these bond eigen-functions have to be found under the characteristic symmetry operations of the group. These operations are in Table I, with the axes shown in (VI).



(VI.)

TABLE I.

Symmetry type.	Rotn. about $x(C_2^x)$.	Rotn. about $y(C_2^y)$.	Rotn. about $z(C_2^z)$.
A_g	+	+	+
B_{1g}	−	−	+
B_{2u}	−	+	−
B_{3u}	+	−	−

The transformation properties of the bond eigen-functions are shown in Table II.

TABLE II.

	Eigen-function.				
Operation.	A_1	B_1	C_1	D_1	E_1
C_2^x	$-A_1$	$-B_1$	$-C_1$	$-D_1$	$-E_1$
C_2^y	$-A_1$	$-B_1$	$-C_1$	$-D_1$	$-E_1$
C_2^z	A_1	B_1	C_1	D_1	E_1

The group representation afforded by the bond eigen-functions can now be broken up into its irreducible representations. This gives

$$\Gamma = 5A_g + 5B_{1g} + 2B_{2u} + 2B_{3u}$$

Tables II allows linear combinations of the bond eigen-functions of the correct symmetry types to be formed. The advantage of using these linear combinations is that matrix elements between two of different symmetry types are zero. Only the B_{1g} and A_g representations are

required, as these contain respectively the ground and the first excited states. The proper linear combinations are

$$B_{1g}: \Psi_{Gs} = N_A(\psi_{A_1} + \psi_{A_2}) + N_B(\psi_{B_1} + \psi_{B_2} + \psi_{B_3} + \psi_{B_4}) + N_C(\psi_{C_1} + \psi_{C_2} + \psi_{C_3} + \psi_{C_4}) + N_D(\psi_{D_1} + \psi_{D_2}) + N_E(\psi_{E_1} + \psi_{E_2})$$

$$A_g: \Psi_{Ex} = N_A'(\psi_{A_1} - \psi_{A_2}) + N_B'(\psi_{B_1} - \psi_{B_2} - \psi_{B_3} + \psi_{B_4}) + N_C'(\psi_{C_1} - \psi_{C_2} - \psi_{C_3} + \psi_{C_4}) + N_D'(\psi_{D_1} - \psi_{D_2}) + N_E'(\psi_{E_1} - \psi_{E_2})$$

The matrix elements between the bond eigen-functions have been found by Pauling's method (*J. Chem. Physics*, 1933, **1**, 280). The following secular equations were obtained for the B_{1g} and the A_g states :

B_{1g} :

3/6	4/12	4/14	2/3	2/5	= 0
4/12	10/10	6/18	4/8	4/10	
4/14	6/18	10/14	2/8	4/10	
2/3	4/8	2/8	3/−2	1/2	
2/5	4/10	4/10	1/2	3/−2	

A_g :

7/6	4/12	4/6	2/−9	2/−3	= 0
4/12	10/6	−2/6	−4/0	2/6	
4/6	−2/6	10/−6	2/0	−4/6	
2/−9	−4/0	2/0	7/−18	1/−6	
2/−3	2/6	−4/6	1/−6	7/−18	

where x/y stands for $x(Q - W) + y\alpha$, W being the energy of the system, Q the Coulomb, and α the exchange integral. Four methods of solution were used : (I) Only the two structures A considered. (II) Structures A and B used, the latter all being given the same coefficient. (III) Structures A and B used, the latter being considered in two groups. (IV) The complete set used. The results are shown in Table III. The transition energy ($B_{1g} \longrightarrow A_g$) has been calculated, using the same approximation for the excited as for the ground state.

TABLE III.

Assumption.	$\frac{E-Q}{\alpha}$	Resonance energy.	Transition energy.	Ground-state wave function. N_a.	N_b.	N_c.	N_d.	N_e.
(I)	2·000	0·50	1·143	0·5773	0	0	0	0
(II)	2·529	1·05	1·102	0·3189	0·0878	0·0878	0	0
(III)	2·559	1·06	0·976	0·3692	0·0655	0·1364	0	0
(IV)	2·597	1·10	0·867	0·3557	0·0704	0·1047	0·0685	0·0276

The best value for the resonance energy is thus $1{\cdot}10\alpha$, and the ground-state wave function has the symmetry properties of B_{1g}.

The bond orders given in Table IV have been found from the calculated energies according to Penney's definition of bond order (*loc. cit.*). The definition depends on a theorem of Dirac, which shows that the energy effects between two electrons due to the quantum-mechanical exchange phenomenon can be dealt with as if they came from a cosine coupling between the electron spins. By dividing the electrons in a complex system into pairs, the electronic energy can be written :

$$W = \text{const.} - \tfrac{1}{2} \sum_{i \neq j} \alpha_{ij}(1 + 4\,\overline{\mathbf{s}_i . \mathbf{s}_j})$$

In this expression, α_{ij} is the exchange integral between the orbitals i and j, and the quantity $\overline{\mathbf{s}_i . \mathbf{s}_j}$ is the scalar product of the spin vectors of the electrons in these orbitals. Binding is greatest when the spins are antiparallel ; the spin product then has the value $-3/4$, corresponding with a bond between the orbitals. If there is no bond, the value is zero. Penney therefore defined the bond order, p_{ij}, as

$$p_{ij} = -4/3\,\overline{\mathbf{s}_i . \mathbf{s}_j}$$

In dealing with π-electron bonds in unsaturated molecules, the π-bond order is therefore 0 for a single bond, 1 for a double bond, and has intermediate values for bonds with partial double-bond character. The meaning of a negative bond order in this scheme is as follows. When the bond order is zero, there is still a repulsive interaction between the electrons, due to the appearance of a constant term in the bracketed part of the energy expression, which is left over when the spin term vanishes. Thus a negative bond order means that there is a repulsion between the electrons greater than given by this constant term. The greatest negative bond order is $-1/3$, when the system of two electrons is in its triplet state, with spins parallel.

To find the bond orders, the energy of the molecule is determined in terms of the α_{ij}'s, and the $\overline{s_i \cdot s_j}$ values obtained. For example, from the fourth entry in Table III,

$$W_{gd.} = \text{const.} + 1{\cdot}7809\alpha_{ab} + 1{\cdot}3790\alpha_{bc} - 0{\cdot}5833\alpha_{ae}$$

where α_{ij} is the exchange integral between atoms i and j. This leads to the bond order $p_{ab} = 0{\cdot}630$, $p_{bc} = 0{\cdot}566$, and $p_{ae} = -0{\cdot}056$. The results to the various approximations are shown in Table IV. The results for the ground state as calculated by the M.O. method are given

TABLE IV.

Approximation.	p_{ab}.	p_{bc}.	p_{ae}.
(I)	0·556	0·556	−0·117
(II)	0·607	0·607	−0·170
(III)	0·627	0·582	−0·130
(IV)	0·630	0·566	−0·056
M.O.	0·524	0·650	0·530

for comparison. It is shown later, however, that the two methods actually describe *different* states as the ground state, so that no agreement between the last entries in each column and the others is to be looked for.

The triplet levels. In order to explore the possibility that the ground state of pentalene might be one having two unpaired electrons, the triplet levels were calculated using the following structures:

A_1 (2). B_1 (2). C_1 (4). D_1 (4). E_1 (4). F_1 (4).

The asterisks indicate the unpaired electrons. The other structures in the set are obtained by rotations around the symmetry axes as shown in Table V. Not all these structures are members of a canonical set. Such a set as is used here has been used for the treatment of naphthalene (Craig, XIth International Congress of Pure and Applied Chemistry, London, 1947), and has the advantage over a canonical set in that there are many equalities among the matrix elements and so the labour of computation is reduced. It is, of course, important to verify that the structures selected are independent. This has been done. All long-bonded structures have been neglected. Structures E and F roughly correspond to the long-bonded structures of the singlet state calculations in that they are destabilised compared with the others by the adjacent electrons with parallel spins.

The transformation properties of the structures are shown in Table V.

TABLE V.

	Eigen-function.					
Operation.	A_1	B_1	C_1	D_1	E_1	F_1
C_2^x	$-A_2$	$-B_1$	C_4	D_4	E_4	F_4
C_2^y	$-A_1$	B_2	C_3	D_3	E_3	F_3
C_2^z	A_2	$-B_2$	C_2	D_2	E_2	F_2

With the aid of the transformation table it can be shown that the reducible representation of the structures breaks up as follows:

$$\Gamma = 4A_g + 5B_{1g} + 5B_{2u} + 6B_{3u}$$

The secular equation thus factors into a sixth-, two fifth-, and one fourth-degree equation. The lowest root is found in the B_{1g} set, and the variation function is

$$\Psi = \mathrm{F}(\psi_{A_1} + \psi_{A_3}) + \mathrm{G}(\psi_{C_1} - \psi_{C_3} - \psi_{C_2} + \psi_{C_4}) + \mathrm{H}(\psi_{D_1} - \psi_{D_3} - \psi_{D_2} + \psi_{D_4}) + \mathrm{I}(\psi_{E_1} - \psi_{E_3} - \psi_{E_2} + \psi_{E_4}) + \mathrm{J}(\psi_{F_1} - \psi_{F_3} - \psi_{F_2} + \psi_{F_4})$$

This leads to the secular equation

$$\begin{vmatrix} 3/-3 & 3/5 & -3/-7 & 2/6 & 0/4 \\ 3/5 & 14/15 & -9/-21 & 6/14 & 8/12 \\ -3/-7 & -9/-21 & 14/15 & 8/16 & 6/9 \\ 2/6 & 6/14 & 8/16 & 10/2 & 2/14 \\ 0/4 & 8/12 & 6/9 & 2/14 & 10/-2 \end{vmatrix} = 0$$

This equation has been solved under the following approximations: (I) Structures E and F excluded: (i) all structures given equal weight (and taken with proper sign); (ii) the full cubic solved. (II) All structures considered: (i) all given equal weight; (ii) structures E and F and the remainder grouped, and the quadratic solved. The results are shown in Table VI.

TABLE VI.

Assumption.	$(E - Q)/\alpha$.	F.	G.	H.	I.	J.
I (i)	1·525	0·1280	0·1280	−0·1280	0	0
I (ii)	1·583	0·0464	0·1377	−0·1445	0	0
II (i)	1·676	0·0830	0·0830	−0·0830	0·0830	0·0830
II (ii)	1·677	0·0872	0·0872	−0·0872	0·0760	0·0760

The lowest triplet level lies above the lowest singlet level by $0{\cdot}920\alpha$.

The Molecular-orbital Treatment.—A molecular orbital is built up from atomic orbitals, one for each carbon atom. This function is used as a basis for a variational treatment. The secular equation will be of the eighth degree, but symmetry may be used to simplify it. The atomic orbitals form a representation of the group D_{2h}, and this may be broken up into its irreducible representations, giving

$$\left.\begin{aligned}\phi_1 &= \psi_a + \psi_e\\ \phi_2 &= \psi_b + \psi_d + \psi_f + \psi_h\\ \phi_3 &= \psi_c + \psi_g\end{aligned}\right\} B_{1u} \qquad \left.\begin{aligned}\phi_4 &= \psi_a - \psi_e\\ \phi_5 &= \psi_b - \psi_d - \psi_f + \psi_h\end{aligned}\right\} B_{3g}$$

$$\left.\begin{aligned}\phi_6 &= \psi_c - \psi_g\\ \phi_7 &= \psi_b + \psi_d - \psi_f - \psi_h\end{aligned}\right\} B_{2g} \qquad \left.\begin{aligned}\phi_8 &= \psi_b - \psi_d + \psi_f - \psi_h\end{aligned}\right\} A_u$$

The secular equation thus factors into a cubic, two quadratics, and a linear equation. The cubic equation, for example, is

$$\begin{vmatrix} x & 2 & 2 \\ 2 & 2(x+1) & 0 \\ 2 & 0 & 2x \end{vmatrix} = 0$$

where $x = (q - e)/\gamma$, q being the Coulomb and γ the resonance integral. The usual neglect of resonance integrals involving non-adjacent atoms and of non-orthogonality of atomic orbitals on different nuclei has been made. Mulliken (*J. Amer. Chem. Soc.*, 1941, **63**, 41) and Wheland (*ibid.*, p. 2025) have shown how this neglect may be avoided. Below are given the four lowest orbitals together with the energies by both the simple (e) and the Mulliken–Wheland (e') treatment:

$$B_{1u}\ \psi_1 = 0{\cdot}4735(\psi_a + \psi_e) + 0{\cdot}3179(\psi_b + \psi_d + \psi_f + \psi_h) + 0{\cdot}2714(\psi_c + \psi_g)$$
$$e_1 = q + 2{\cdot}343\gamma \qquad e_1' = q' + 1{\cdot}480\beta$$

$$B_{2g}\ \psi_2 = 0{\cdot}5000(\psi_c - \psi_g) + 0{\cdot}3535(\psi_b + \psi_d - \psi_f - \psi_h)$$
$$e_2 = q + 1{\cdot}414\gamma \qquad e_2' = q' + 1{\cdot}041\beta$$

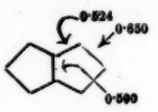
$$B_{3g}\ \psi_3 = 0{\cdot}5774(\psi_a - \psi_e) - 0{\cdot}4082(\psi_b - \psi_d - \psi_f + \psi_h)$$
$$e_3 = q + 1{\cdot}000\gamma \qquad e_3' = q' + 0{\cdot}800\beta$$

$$B_{1u}\ \psi_4 = -0{\cdot}4560(\psi_a + \psi_e) - 0{\cdot}1207(\psi_b + \psi_d + \psi_f + \psi_h) - 0{\cdot}5125(\psi_c + \psi_g)$$
$$e_4 = q + 0{\cdot}471\gamma \qquad e_4' = q' + 0{\cdot}421\beta$$

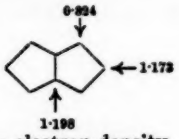
The total energy of the molecule in its ground state is thus $8q + 10{\cdot}456\gamma$, or $8q' + 7{\cdot}484\beta$, the resonance energy being $2{\cdot}456\gamma$ or $1{\cdot}084\beta$. The M.O. method, of course, describes as totally symmetrical the state of lowest energy, for in that state all the orbitals are doubly filled, and all therefore contribute a totally symmetrical part to the molecular wave function.

Coulson and Rushbrooke (*loc. cit.*) have examined pentalene in the molecular-orbital approximation, and the bond orders which come from their results are shown in the diagram below. They point out, however, that the molecular-orbital treatment cannot be carried through in a satisfactory way for any of the molecules pentalene, azulene, or heptalene, for in all these cases the method finds that the π electrons are not uniformly distributed over the carbon atoms, but tend to accumulate at certain points at the expense of others. The distribution

found for pentalene by Coulson and Rushbrooke is shown in the diagram below. Such a difficulty can only arise in the valence-bond method when polar structures are taken into account;



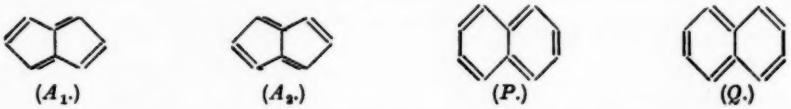
Bond orders.



π electron density.

otherwise all the states must have exactly one π electron per carbon atom. In other words the valence-bond method encounters no difficulty of procedure to match that encountered here by the M.O. method.

Discussion of the Results.—The most striking difference between the two methods is the predicted symmetry of the ground and the first excited state. The non-totally symmetrical ground state for pentalene in the valence-bond method arises from the fact that under the conditions which give the ground state as a sum of canonical structures, structure A_1, for example, is transformed into $-A_2$ by rotation about the x and y axes. This is to be compared



(A_1.) (A_2.) (P.) (Q.)

with the case of naphthalene, which is typical of all hydrocarbons built up from six-membered rings and for which (P) goes into (Q) under the second of these operations. The same discrepany between the two methods of treatment is met with in *cyclo*butadiene and the planar model of *cyclo*octatetraene. In the M.O. treatment it is readily seen that this method *must* lead to a totally symmetrical ground state, except in those cases where orbital degeneracy occurs. This is the case, for example, in *cyclo*butadiene (Wheland, *Proc. Roy. Soc.*, 1938, **164**, *A*, 397), in which the orbital of lowest energy is of symmetry A_{2u}, and then there is a pair of degenerate orbitals of symmetry E_g. The lowest state thus has the symmetry $(A_{2u})^2(E_g)^2$, so that if the orbital degeneracy were removed the four states would have the symmetries A_{1g}, A_{2g}, B_{1g}, and B_{2g}. A more complete treatment, *i.e.*, the inclusion of electron repulsion, would remove the degeneracy and separate the above four levels.

Another aspect of the same problem is the lack of self-consistency in the M.O. treatment, which is brought to light by the appearance of charge separation. The reason for this is readily understood by a consideration of what in the V.B. method would be called polar structures. For a molecule like naphthalene the structures shown below have equal coefficients in the M.O. wave function :

However, for pentalene the corresponding two structures come into the molecular wave function with unequal coefficients, giving a net charge drift. The difficulty then arises because of the over-emphasis placed on structures involving charge separation by the M.O. method. The V.B. method, with its neglect of polar structures, does not lead to any inconsistency. In view of the different symmetries of the ground states predicted by the two methods there is no point in carrying the comparison between the states further.

The same symmetry difficulty is found with heptalene : again the ground and first excited states in the V.B. approximation have the symmetries B_{1g} and A_g, respectively. In azulene, there is only a single axis of symmetry and the ground state of this molecule is symmetric to rotation around the axis. Thus *cyclo*butadiene, pentalene, and heptalene are singled out from naphthalene and azulene in that their ground states are not totally symmetrical. In speaking of a non-totally symmetrical ground state it is, of course, not implied that the electron distribution is unsymmetrical, for the V.B. method cannot give that result. The difference between pentalene and naphthalene in their ground states is that the wave function for the first changes sign under certain symmetry operations, whereas for naphthalene it is invariant.

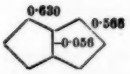
The energy levels and bond orders are summarised below.

$Q + 1{\cdot}68\alpha$ — $^3B_{1g}$

$Q + 1{\cdot}73\alpha$ — $^1A_{1g}$

$Q + 2{\cdot}60\alpha$ — $^1B_{1g}$

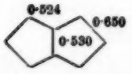
V.B.



$8q' + 7{\cdot}063\beta$ — $^1B_{1g}$, $^3B_{1g}$

$8q' + 7{\cdot}484\beta$ — $^1A_{1g}$

M.O.



The small negative bond order obtained by the Penney method for the bond between the atoms common to the two rings indicates that there is a weak repulsive interaction exerted by the π electrons across this bond. However, the magnitude of the resonance energy ($1{\cdot}10\alpha$) shows that the interaction of the π electrons as a whole is quite strongly stabilising—not much less, per electron, than in benzene. The resonance splitting between the ground and the first excited state is such as to suggest a long wave-length absorption band at about 6600 A., so that the molecule would be deeply coloured according to the V.B. theory.

The M.O. treatment of pentalene and heptalene is inconsistent. There is, however, no evident difficulty with the V.B. method, which can be carried through just as for an " ordinary " molecule. If therefore it can be concluded that the V.B. is here the more reliable account, pentalene should have a considerable resonance energy, about the same, per π electon, as azulene and a little less than benzene. The symmetry of the ground state is a qualitative feature which distinguishes pentalene and heptalene from known hydrocarbons, but it is not clear what connection this has with the fact that these molecules have neither been found in Nature nor prepared chemically.

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208. *The Electronic Structure of Some Aza-derivatives of Naphthalene, Anthracene, and Phenanthrene.*

By H. C. LONGUET-HIGGINS and C. A. COULSON.

Theoretical calculations are made of the distribution of π-electrons in a number of mono- and di-aza-derivatives of naphthalene, anthracene, and phenanthrene. Relative values are given for the net charges at different positions in such molecules, and these are found to be closely correlated with the chemical behaviour of such molecules in substitution reactions, especially by anionoid reagents. The method of calculation employed leads naturally to the idea that the effects of successive substitutions should be approximately additive, in agreement with experiment. A discrepancy is pointed out between estimated and observed basic strengths, and it is suggested that the electric moment of a monoaza-hydrocarbon and changes in certain resonance integrals on quarternation may be important in determining its basic strength.

IT was pointed out by Wheland and Pauling (*J. Amer. Chem. Soc.*, 1935, **57**, 2091) that the reactivity of heteroaromatic systems towards anionoid and cationoid reagents was closely correlated with the π-electron distributions in such molecules, as determined by the method of molecular orbitals, if certain reasonable values were assigned to the energy parameters. More recently, we have successfully extended such calculations to quite complex systems containing nitrogen atoms (*Trans. Faraday Soc.*, 1947, **43**, 87), and have given a simple theoretical interpretation to the undoubted correlation between the calculated electron distributions and the observed chemical behaviour (*Proc. Roy. Soc.*, 1947, *A*, **191**, 39; **192**, 16).

In calculating the π-electron distribution in an unsaturated molecule, it is usual to begin by assuming that each π-electron moves in a molecular orbital ψ_j which can be expressed in the form

$\Sigma_r c_{rj}\,\phi_r$, where ϕ_1, ϕ_2, . . . are appropriate atomic orbitals associated with atoms 1, 2, . . . of the system. The coefficients c_{rj} and the possible molecular orbital energies are then determined by solution of a set of linear equations called the secular equations. If the molecular orbitals ψ_1, ψ_2, . . . are numbered in order of increasing energy, and there are $2n$ π-electrons in the system, then the mean number of π-electrons in the atomic orbital ϕ_r is given by

$$q_r = 2\sum_{j=1}^{n} c_{rj}^2$$

and it is this quantity, conveniently designated as the electron density at position r, which has been found to be principally important in determining the reactivity of the position towards heterolytic reagents.

The labour involved in the straightforward calculation of q_r is comparatively slight for small or highly symmetrical molecules, but becomes very considerable for unsymmetrical molecules with more than about ten atomic orbitals. However, it is not difficult to obtain approximate values for q_r in quite large molecules with the aid of first-order perturbation theory. This method of calculation was discussed by Wheland and Pauling (*loc. cit.*), but has not been very widely used hitherto. In this paper we shall present and discuss the results of such calculations on a number of aza-derivatives of naphthalene, anthracene, and phenanthrene.

Method.—The coefficients, c_{rj}, and therefore the electron densities q_r, in an unsaturated molecule, are determined completely by the values of certain energy integrals α_s and β_{tu} (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, **1947**, *A*, **191**, 39), so in calculating the π-electron distribution in an aza-hydrocarbon we may proceed as follows: We start with the parent hydrocarbon, and find its electron densities, q_r^0, say. Replacement of the group $\gg$CH by $\gg$N or $\gg$C$-$ by $\gg\overset{+}{\mathrm{N}}-$ will alter some of the energy integrals α_s and β_{tu} upon which the electron densities depend. If this alteration is not very large, the electron densities in the aza-hydrocarbon will be given approximately by the equation

$$q_r = q_r^0 + \sum_s \left(\frac{\partial q_r}{\partial \alpha_s}\right)^0 (\alpha_s - \alpha_s^0) + \sum_{t,u} \left(\frac{\partial q_r}{\partial \beta_{tu}}\right)^0 (\beta_{tu} - \beta_{tu}^0) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where q_r, α_s, and β_{tu} refer to the aza-hydrocarbon, and the superscript denotes quantities referring to the parent hydrocarbon; that is to say, we may use first-order perturbation theory to calculate q_r, taking the parent hydrocarbon as basis.

The formal definitions of α_s and β_{tu} are as follows: α_s, which is conveniently described as the Coulomb term for atom s, is defined by the equation

$$\alpha_s = \int \phi_s \mathrm{H} \phi_s \mathrm{d}\tau = \int \phi_c \mathrm{H} \phi_c \mathrm{d}\tau$$

H being the effective Hamiltonian operator for a single electron, and ϕ_c being the $2pz$ orbital of a carbon atom in benzene. It is usual to assume that α_s is zero for every unsaturated carbon atom in a hydrocarbon, and that in general its value depends only on the chemical nature of atom s and its nearest neighbours; β_{tu}, on the other hand, is defined by the equation

$$\beta_{tu} = \int \phi_t \mathrm{H} \phi_u \mathrm{d}\tau$$

and is very small indeed when atoms t and u are not bonded. For this reason it is described as the resonance integral of the bond tu. Like α_s, its value is assumed to depend only on the chemical nature of atoms t and u; in particular, it is generally assigned a fixed value β for all aromatic carbon–carbon bonds.

Now, in certain circumstances equation (1) can be considerably simplified. If the given aza-compound is derived from an unsaturated hydrocarbon containing no odd-membered rings, then it can be shown that $q_r^0 = 1$ (Coulson and Rushbroke, *Proc. Camb. Phil. Soc.*, **1940**, **36**, 193) and that $(\partial q_r/\partial \beta_{tu})^0 = 0$ (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, **1947**, *A*, **192**, 16). Further, from the arguments of the preceding paragraph, $\alpha_s^0 = 0$ for every unsaturated carbon atom in a hydrocarbon. Equation (1) therefore takes the form

$$q_r = 1 + \sum_s \pi_{r,s}^0 \alpha_s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $\pi_{r,s}^0$ stands for $(\partial q_r/\partial \alpha_s)^0$, and is the quantity known as the mutual polarisability of atoms r and s in the hydrocarbon. It is convenient to express $\pi_{r,s}^0$ in the form $x_{r,s}\beta$, and α_s in the

form $y_s\beta$, where $x_{r,s}$ and y_s are dimensionless; the net positive charge $1 - q_r$ at atom r in the aza-compound is then given by the equation

$$1 - q_r = -\sum_s x_{r,s}y_s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

measured in units of the electronic charge.

Comparison of Methods of calculating q_r.—Equation (3) tells us that if we can find the values of $x_{r,s}$ for the hydrocarbon, and have some means of estimating the numbers y_s for the aza-derivative, we can calculate very simply the approximate net charges at the various atoms of the aza-compound.

At first sight it might be thought that finding the terms $x_{r,s}$ for a hydrocarbon would be almost, if not quite, as laborious as direct solution of the secular equations for one of its aza-derivatives. However, it often happens that the hydrocarbon is more symmetrical than the derivative—for instance, naphthalene is more symmetrical than quinoline—and this makes the former process considerably easier. Further, if we are interested in the electron densities in a number of derivatives of the same hydrocarbon, the perturbation method outlined in the last section enables us to calculate all these distributions very quickly once the quantities $x_{r,s}$ are known. For example, direct solution of the secular equations for an unsymmetrical aza-anthracene requires about a fortnight; whereas by first-order perturbation theory approximate values can be obtained for the electron densities in 20 or 30 such molecules within a week, starting *ab initio*.

Although in principle the perturbation method is less accurate than direct solution of the secular equations for giving the net charges $1 - q_r$, both methods are open to the severe objection that values must be guessed for the Coulomb terms α_s in the aza-compounds, so there is less to choose between the two methods than might at first appear. Further, it is the relative values of the electron densities or net charges that are of primary interest to the chemist, and it has been found that the two methods of calculation give consistent results in this respect, provided the same values are assigned to the Coulomb integrals. In any case, there is reason to suppose that the uncertainty in the Coulomb integral for heteroaromatic nitrogen gives rise to a probable error in the absolute magnitudes of the net charges which far exceeds that due to the use of first-order perturbation theory.

Values of $x_{r,s}$ *for Naphthalene, Anthracene, and Phenanthrene.*—In Tables I, II, and III are given values of $x_{r,s}$ for naphthalene, anthracene, and phenanthrene, as all these molecules have

Naphthalene.

Anthracene.

Phenanthrene.

hetero-derivatives for which the calculation of electron densities would be of interest from the chemical point of view. (The numbering used is shown in the attached formulæ.) The figures given for $x_{r,s}$ have been calculated on the assumption that all the carbon–carbon resonance integrals are equal to β, and using the equations given for the calculation of $\pi_r^0{}_{,s}$ by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1947, *A*, **191**, 39). It should be remembered that $x_{r,s} = x_{s,r}$.

TABLE I.

Mutual atom polarisabilities in naphthalene (the figure given is $x_{r,s} = \beta \times \pi_{r,s}$).

$s =$	1.	2.	9.	$s =$	1.	2.	9.
$r = 1$	0·443	−0·213	−0·089	$r = 6$	0·007	−0·033	−0·089
2	−0·213	0·405	0·007	7	−0·033	0·000	0·007
3	0·018	−0·110	−0·049	8	0·027	−0·033	−0·089
4	−0·139	0·018	0·004	9	−0·089	0·007	0·330
5	−0·023	0·007	0·004	10	0·004	−0·049	−0·077

TABLE II.

Mutual atom polarisabilities in anthracene (the figure given is $x_{r,s}$).

$s =$	1.	2.	9.	13.	$s =$	1.	2.	9.	13.
$r = 1$	0·4540	−0·2306	0·0428	−0·0777	$r = 8$	0·0080	−0·0106	0·0428	−0·0179
2	−0·2306	0·4108	−0·0544	0·0088	9	0·0428	−0·0544	0·5257	−0·1249
3	0·0220	−0·0990	0·0142	−0·0364	10	−0·0402	0·0142	−0·2175	0·0085
4	−0·1512	0·0220	−0·0402	0·0027	11	0·0033	−0·0176	0·0085	−0·0261
5	−0·0084	0·0040	−0·0402	0·0033	12	−0·0179	0·0000	−0·1249	0·0053
6	0·0040	−0·0124	0·0142	−0·0176	13	−0·0777	0·0088	−0·1249	0·3313
7	−0·0106	0·0010	−0·0544	0·0000	14	0·0027	−0·0364	0·0085	−0·0593

TABLE III.

Mutual atom polarisabilities in phenanthrene (the figure given is $x_{r,s}$).

$s=$	1.	2.	3.	4.	10.	11.	12.
$r=1$	0·4391	−0·1935	0·0177	−0·1209	0·0242	−0·1025	0·0033
2	−0·1935	0·4028	−0·1235	0·0152	−0·0146	0·0076	−0·0633
3	0·0177	−0·1235	0·4068	−0·1892	0·0079	−0·0609	0·0098
4	−0·1209	0·0152	−0·1892	0·4292	−0·0080	0·0041	−0·1105
5	0·0001	−0·0118	0·0021	−0·0170	0·0042	−0·0121	0·0147
6	−0·0083	0·0002	−0·0091	0·0021	−0·0423	0·0002	−0·0131
7	0·0006	−0·0107	0·0002	−0·0118	0·0002	−0·0128	0·0036
8	−0·0098	0·0006	−0·0083	0·0001	−0·0450	0·0036	−0·0086
9	−0·0449	0·0002	−0·0422	0·0042	−0·2699	0·0126	−0·0553
10	0·0242	−0·0146	0·0079	−0·0080	0·4424	−0·0637	0·0070
11	−0·1026	0·0076	−0·0609	0·0041	−0·0637	0·3335	−0·0911
12	0·0033	−0·0633	0·0098	−0·1106	0·0070	−0·0911	0·3494
13	−0·0086	0·0036	−0·0131	0·0147	−0·0553	0·0003	−0·0488
14	0·0036	−0·0128	0·0002	−0·0120	0·0126	−0·0213	0·0003

These figures illustrate well the law of alternating polarity, which requires $\pi_{r,s}$ to be positive or negative according as atoms r and s are separated by odd or even numbers of bonds, and also the general tendency for interactions between distant atoms to be smaller than interactions between atoms in the same ring. In fact, there is a close resemblance between the interactions in the terminal rings of phenanthrene and anthracene and the interactions in naphthalene.

Values of the Coulomb Terms.—The evaluation of the terms y_s ($= \alpha_s/\beta$) is a much more uncertain business than the calculation of $x_{r,s}$. If the Coulomb term for nitrogen is denoted by α_N, and that of an adjacent carbon atom by α', then the ratio of α_N to α' can be estimated roughly from the relative reactivities of the different positions in pyridine, say. In this way Wheland and Pauling showed that this ratio must be of the order of 8 : 1, and this is the figure we shall adopt. On the other hand, the value of α_N/β ($= y_N$, say) is extremely uncertain. For example, if we take the values $y_N = 2$, $y' = \frac{1}{2}$ for pyridine, as suggested by Wheland and Pauling, we find that the calculated dipole moment in pyridine due to the π-electrons is about 4·8 D., depending slightly on the angle assumed at the nitrogen atom. If we add to this the moment of the single C–N σ bonds (estimated at about 0·8 D.) and the moment of the lone-pair electrons on the nitrogen atom (estimated at about 0·5 D.), we obtain a theoretical value for the total moment of about 6·1 D., whereas the observed moment is actually 2·2 D. This enormous discrepancy must mean either that the above values of y_N and y' are much too large, or that some further effect has been neglected in the calculation. For example, there might be an induced moment in the σ-bonds due to the uneven distribution of the π-electrons; such an induced moment would act in the opposite direction to the π-electron moment, and might reduce the total moment of the molecule considerably below what it would otherwise be. That such " back-polarisation " does in fact occur is strongly suggested by the fact that even in a saturated zwitterion such as betaine the observed dipole moment is less than half what would be expected from the formal charge displacement (Sutton, private communication). Fortunately, however, the absolute values of the terms y_s are not important for the present investigation: it will be seen from equation (3) that multiplication of all of them by a constant factor k merely multiplies the net charges by the same factor k, without altering their ratios.

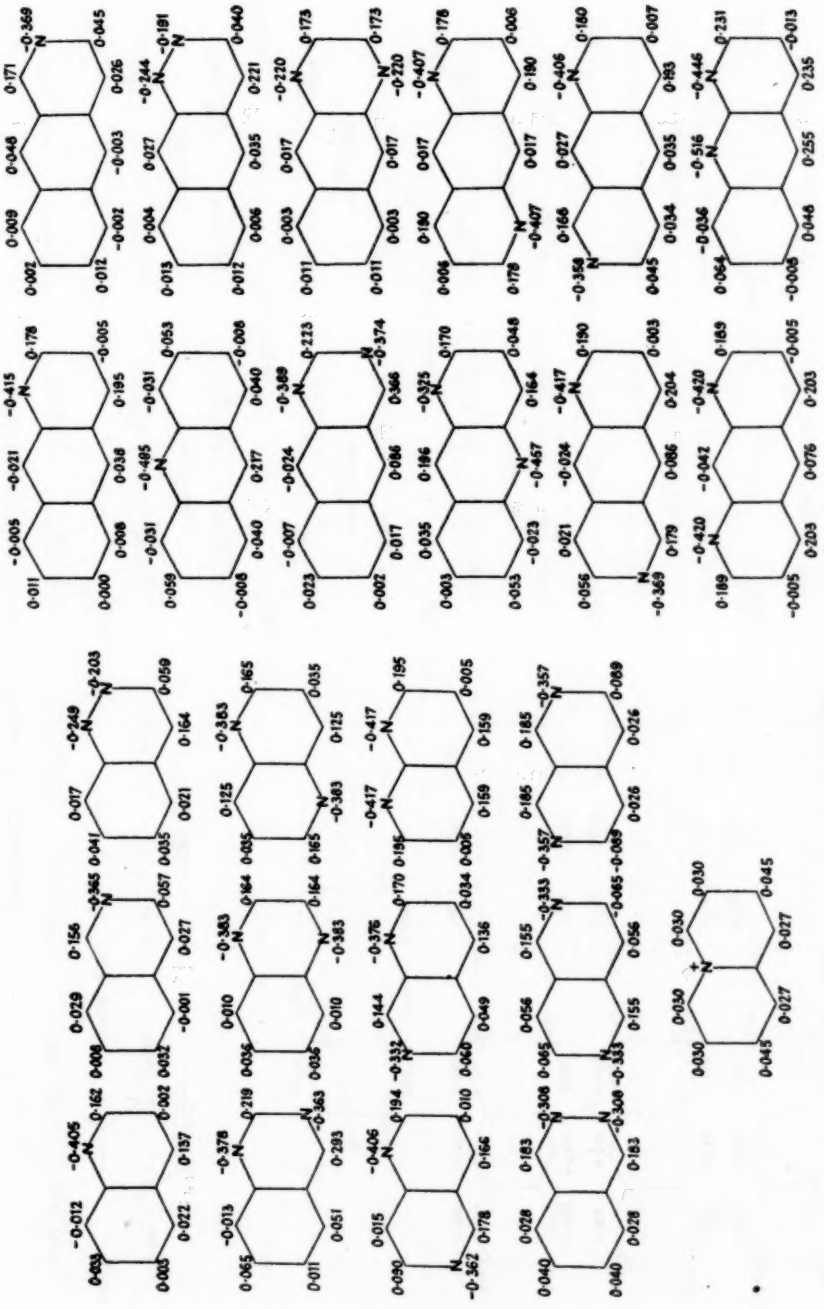
Results.—In calculating the net charges in the monoaza-hydrocarbons it has been assumed that α_N/α' ($= y_N/y'$) is equal to 8; and the net charges are expressed as multiples of y_N; that is to say, the figures given in the following lists would be equal to the net charges if α_N were equal to β, and α' equal to β/8.

In the diaza-hydrocarbons it has been assumed that the perturbations due to the two nitrogen atoms are additive; this is equivalent to assuming that the terms y_s are in the following ratios:

$$y_N : y_N' : y' : y'' = 8 : 9 : 1 : 2$$

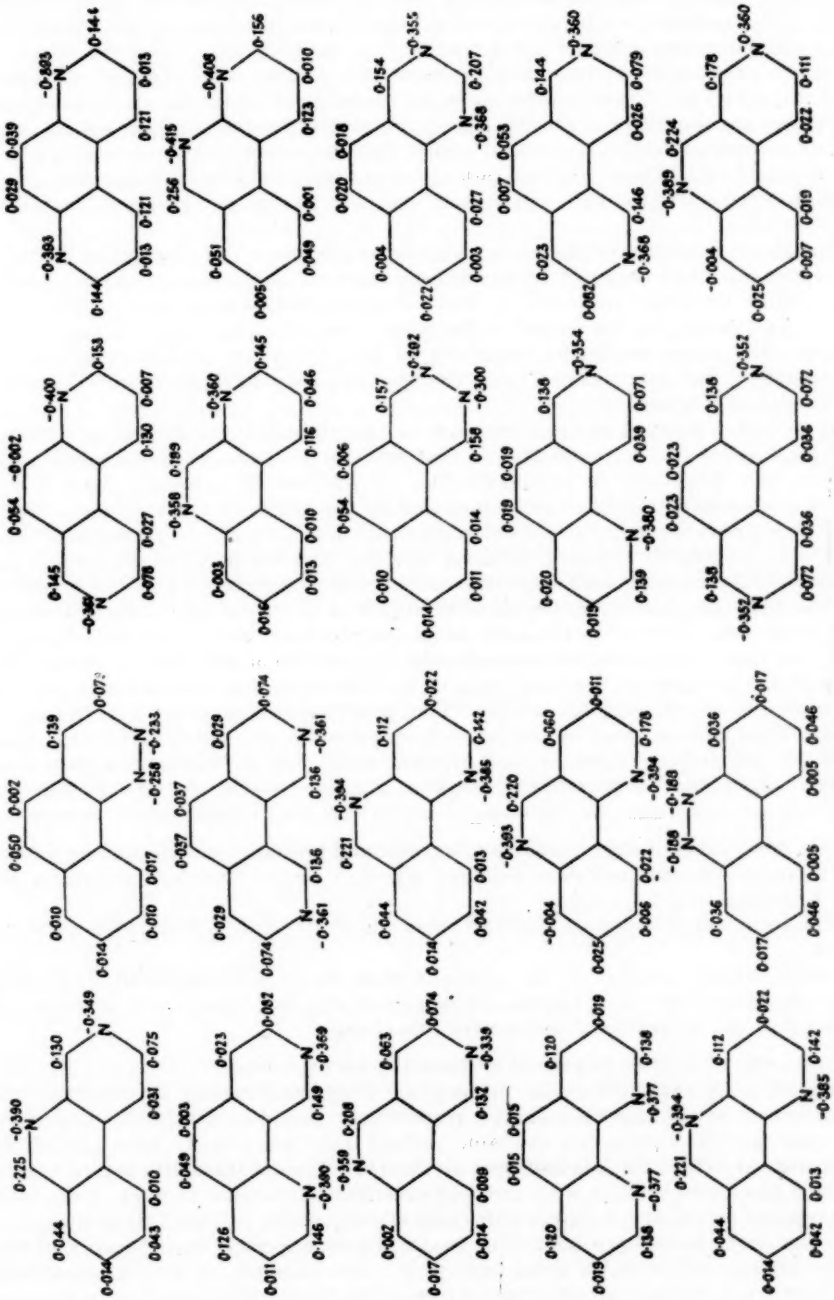
where y_N' refers to a nitrogen atom bonded to another nitrogen atom, y' refers to a carbon bonded to one nitrogen, and y'' to a carbon bonded to two nitrogens. This assumption implies that the net charges in a diaza-hydrocarbon should be the sum of the net charges for the corresponding two monoaza-hydrocarbons, which is likely to be true on almost any reasonable hypothesis.

The figures given in the accompanying diagrams are the relative net charges at the external positions of all the mono- and di-aza-naphthalenes, -anthracenes, and -phenanthrenes. For completeness we have included the four cations which arise from replacing the interior carbon



Aza-derivatives of naphthalene and anthracene.

Aza-derivatives of anthracene (contd.) and phenanthrene.



Aza-derivatives of phenanthrene (contd.).

atoms in these molecules by N^+. The relation of these figures to the known chemistry of these molecules is discussed in the next section.

Discussion of Results.—On the assumption that the net charges are of primary importance in determing the substitutive behaviour of a heteroaromatic molecule one would draw the following general conclusions from the accompanying figures: First, that the effects of aza-substitution on an aromatic hydrocarbon die away with distance from the seat of substitution; one would therefore expect considerable chemical resemblances between, say, 1-aza-anthracene on the one hand and quinoline on the other, especially in the reactions of their heterocyclic rings. Secondly, as mentioned earlier, one would expect that the effects of two or more replacements of CH by N should be additive; this is a quite general conclusion following from the assumption that one such replacement has sufficiently small effects to be regarded as a perturbation applied to the hydrocarbon.

Both the above general expectations are verified in practice. An example of the first is the three diazaphenanthrenes obtained by the Skraup reaction on *o*-, *m*-, or *p*-phenylenediamine, which all closely resemble quinoline in their electron distributions and in their chemical properties. An example of the second is the series: naphthalene, 1-aza-, 3-aza-, 1 : 3-diaza-naphthalene; along this series the reactivity of the 4-position towards anionoid reagents increases steadily; and other examples of the approximate additivity of substitutive effects could be multiplied indefinitely.

Coming to a more detailed analysis, one finds on the whole that the greater the net charge at a given carbon atom the more reactive is that position to anionoid (nucleophilic) reagents. For example, the 9-position in phenanthridine is particularly sensitive towards anionoid reagents: 9-aminophenanthridine can be prepared by the sodamide reaction in excellent yield. Associated with this is the activity of 9-chlorophenanthridine, which will condense with amines, etc., under only moderately drastic conditions, and the high reactivity of the methyl group at this position, which condenses with aldehydes and is readily oxidised; for instance, oxidation of 1 : 3 : 9-trimethyl-2-azaphenanthridine leads to attack of the 9-methyl group in preference to the others, with separation of an insoluble azaphenanthridone, which thereby escapes further oxidation. All these phenomena are characteristic of positions of low electron density (high net charge), as is the prototropic rearrangement of the corresponding hydroxy-derivative to give a stable molecule of the pyridone type. This prototropic change is characteristic of the 2-hydroxypyridine residue, and occurs in such compounds as *iso*quinoline, etc. Examples of this last are *iso*quinolone, acridone, and cyanuric acid. On the assumption that a position becomes markedly active to electrophilic reagents when the relative net charge there exceeds about 0·2, one may formulate the following rules for the aza-hydrocarbons investigated:

(1) In the derivatives of naphthalene, anthracene, and phenanthrene containing a 1-nitrogen atom, the 2- and 4-positions will show anionoid activity; and in those containing a 2-nitrogen atom the 1-position will be active.

(2) 9-Aza-anthracenes and 9-azaphenanthrenes will show strong anionoid reactivity at their 10-positions.

(3) If the Coulomb integral of the nitrogen atom in an aza-compound is increased by quaternary alkylation, the reactivity of a position of high net charge will be enhanced still further, owing to the proportional increase in this charge.

These rules are, of course, in general agreement with experience.

In substitution by cationoid or by nucleophilic reagents it would be expected that the positions of lowest or of highest net charge, respectively, would be attacked. Unfortunately, not much experimental evidence is available beyond what has already been quoted, but, in general, experiment follows the line indicated by theory. The situation with regard to cationoid substitution is less clear-cut than with anionoid substitution, because in most of the molecules listed the positions of lowest net charge differ only slightly in the values of these charges. This means that any errors in the approximations used will assume greater importance, and also that second-order effects will probably come into play. For example, in 1 : 7-diazanaphthalene, where the lowest net charges are 0·034 and 0·049 at the 3- and the 5-position, respectively, it might easily happen that the 5-position would be more easily nitrated than the 3-position owing to greater ease of polarisation there; for it is known that in naphthalene itself the α-positions have greater self-polarisability than the β-positions. It has been shown that effects of this type become important when differences in electron density are very small, so it would be surprising if there were no discrepancies between theory and experiment as far as cationoid activity is concerned.

There is one discrepancy, which must be pointed out, between the basicities of some of these molecules and the calculated net charges at their nitrogen atoms. According to figures for the relative net charges, one would expect the basic strengths of pyridine, quinoline, and acridine to increase in that order; in fact their pK_a values in water at 20° are 5·2 (Britton and Williams, *J.*, 1935, 796), 4·8 (Albert, *Nature*, 1944, **153**, 467), and 4·3 (Albert, Rubbo, and Goldacre, *ibid.*, 1941, **147**, 332), respectively. Strictly, of course, one should compare the electron densities with the heats rather than the free energies of ionisation, but it seems unlikely that the entropies of ionisation differ very much between these bases, so the anomaly must be regarded as real. It is possible that the anomaly is connected with the fact that the dipole moments of these bases are in the opposite order to what would be expected from their π-electron distributions; the observed moments are 2·21, 2·14, and 1·95 D., respectively. It seems quite likely therefore that the basic strength of a monoaza-hydrocarbon depends largely on its dipole moment; and if this is so then any error in the calculation of the dipole moment (see earlier) would appear as a corresponding error in the estimated value of the basic strength. There is clearly scope for further investigation of such a relationship.

Added, December 17th, 1948.—Since this paper was submitted for publication, a suggestion has come to our notice (Dyatkina, *Doklady Akad. Nauk. U.S.S.R.*, 1948, **59**, 517) that the basic strength of an aza-hydrocarbon depends on the change of resonance integral in the C–N bonds when a proton is attached to the nitrogen atom. In this paper we have assumed that the change in $\mathcal{E}$, the energy of the mobile electrons, upon addition of a proton to the nitrogen atom, depends solely upon the change in α_N, the Coulomb term for the nitrogen atom, according to the equation

$$\delta\mathcal{E} = (\partial\mathcal{E}/\partial\alpha_N)\delta\alpha_N = q_N\delta\alpha_N$$

If this were so, the basic strength of a heterocycle should be greater the greater the value of q_N; and, as already mentioned, this prediction is at variance with the experimental facts. The discrepancy may, however, be resolved by following Dyatkina, and writing

$$\begin{aligned}\delta\mathcal{E} &= \frac{\partial\mathcal{E}}{\partial\alpha_N}\delta\alpha_N + \sum_t \frac{\partial\mathcal{E}}{\partial\beta_{tN}}\delta\beta_{tN} \\ &= q_N\delta\alpha_N + 2\sum_t p_{tN}\delta\beta_{tN}\end{aligned}$$

where t denotes an atom bonded to the nitrogen atom, and p_{tN} is the mobile order of the bond t–N. In this equation q_N equals $1 - Q_N y_N$, where Q_N is the relative net charge on the nitrogen atom, and $y_N = \alpha_N/\beta$. Hence

$$\delta\mathcal{E}/\beta = (1 - Q_N y_N)\delta y_N + 2\sum_t p_{tN}\delta z_{tN}$$

where $\delta y_N = \delta\alpha_N/\beta$ and $\delta z_{tN} = \delta\alpha_{tN} = \delta\beta_{tN}/\beta$.

In this equation δy_N, y_N, δz_{tN}, and p_{tN} are positive quantities, and $\delta\mathcal{E}$, β, Q_N are negative; hence the magnitude of $\delta\mathcal{E}$ (and hence the basic strength of the heterocycle) varies in the same direction as that of the expression

$$-Q_N y_N + 2\sum_t p_{tN}\frac{\delta z_{tN}}{\delta y_{tN}} = D, \text{ say}$$

Values of Q_N are given in the diagrams above, and the mobile bond orders p_{tN} are nearly the same as in the parent hydrocarbons (see Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **192**, 16). One may therefore tabulate values of D for different values of y_N and $\delta z_{tN}/\delta y_{tN}$ as follows:

Data on basic strengths of some heterocycles (see text).

	$-Q_N$.	$2\Sigma p_{tN}$.	D_1.	D_2.	D_3.	D_4.
Pyridine	0·359	2·667	0·359	0·447	0·642	1·405
Quinoline	0·405	2·560	0·405	0·459	0·633	1·361
Acridine	0·495	2·424	0·495	0·490	0·633	1·311

D_1 is the value of D when $y_N = 1·0$, $\delta z_{tN}/\delta y_{tN} = 0·0$
D_2 ,, ,, ,, $= 0·5$, ,, $= 0·1$
D_3 ,, ,, ,, $= 0·3$, ,, $= 0·2$
D_4 ,, ,, ,, $= 0·2$,, $= 0·5$

Clearly, if $\delta z_{tN} = 0$, the basicity is governed entirely by Q_N, as we originally supposed, and acridine should be more basic than pyridine; but if $\delta z_{tN}/\delta y_{tN}$ is comparable to y_N, the theoretical order of basicity in the above series is reversed, and pyridine should be the most

basic, as observed. Unfortunately, as pointed out earlier, there is no independent means of estimating y_N or $\delta z_{tN}/\delta y_{tN}$ at present, so this theory can hardly be claimed to explain the observed basic strengths. However, considerations of this type may account for the breakdown of the very simple approach, since it is not unreasonable to suppose that the change in β_{tN} on addition of a proton is comparable with y_N times the change in α_N.

Our thanks are due to Mr. H. Greenwood for checking some of the calculations, and to Dr. L. E. Sutton and Dr. V. Petrow for helpful discussion.

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209. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part IV.* β-*Succinic Acid.*

By J. D. MORRISON and J. MONTEATH ROBERTSON.

The parameters of the β-succinic acid crystal structure have been re-determined with the use of more complete Fourier series and the preparation of a new projection of the structure along the [101] crystal axis. Small shifts in the atomic positions are obtained, but the slight shortening of the carbon–carbon bonds below the standard value of 1·54 A. reported by Verweel and MacGillavry is confirmed. The present results indicate, however, that the shortest bond (1·50 A.) is that between the central pair of carbon atoms. The situation of this bond is similar to that of the central bond in dibenzyl and to that of the bond in geranylamine hydrochloride which is situated centrally between the two ethylene linkages. In both these cases a similar contraction has been observed. The intermolecular approach distances in the succinic acid structure are also discussed.

THE physical properties of the normal aliphatic dicarboxylic acids have already been the subject of numerous studies and a large amount of data has been collected for this series. Interest has been stimulated by the curious alternating effects which are a feature of homologous series of normal aliphatic compounds in general. These effects are shown to a greater or less extent by the hydrocarbons, alcohols, ketones, diamines, etc., but in none to the same degree as in the normal aliphatic dibasic acids. Numerous theories have been proposed (Malkin, *J.*, 1931, 2796; Muller, *Proc. Roy. Soc.*, 1929, *A*, **124**, 317; Nekrassow, *Z. physikal. Chem.*, 1927, **128**, 203) to account for the variation in properties of the odd and even members, but to a large extent these theories have remained speculative for want of a sufficiently detailed knowledge of the structures involved.

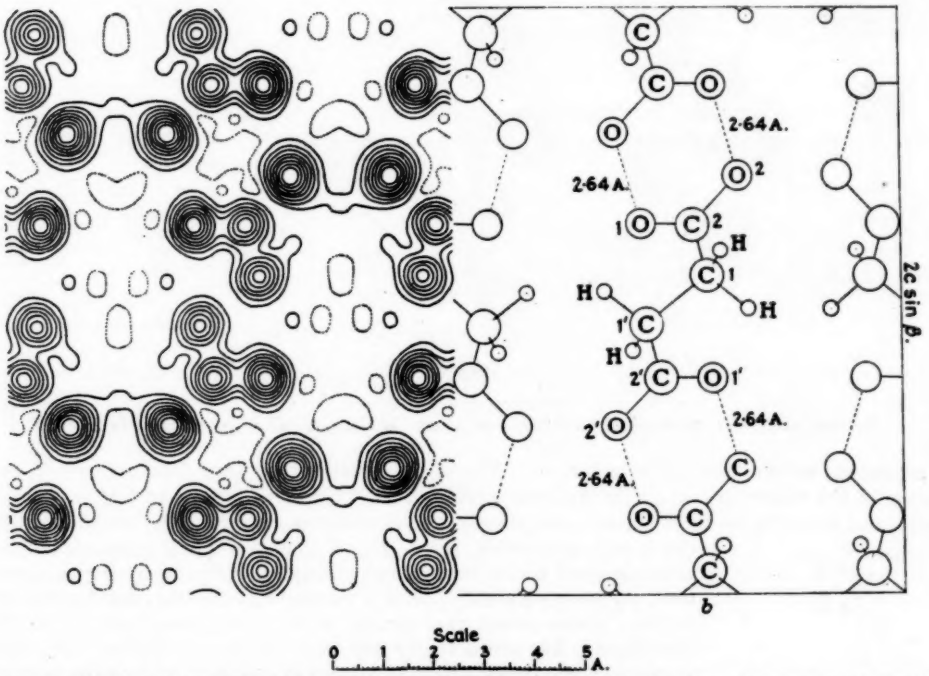
The object of the present series of papers will be to determine the crystal and in particular the detailed molecular structures of some of the simple members of this series with as much accuracy as possible in an endeavour to obtain a reliable correlation between structure and properties. Good crystals are easily obtained and unit-cell and space-group determinations are already available for most of the common members (Caspari, *J.*, 1928, 3235; 1929, 2709; Gerstäcker, Moller, and Reis, *Z. Krist.*, 1927, **66**, 421). More detailed *X*-ray structural investigations have also been made for anhydrous oxalic acid (Hendricks, *ibid.*, 1935, **91**, 48), the dihydrate of oxalic acid (Part I of this series, Dunitz and Robertson, *J.*, 1947, 142), succinic acid (Verweel and MacGillavry, *Nature*, 1938, **142**, 161; *Z. Krist.*, 1939, **102**, 60), and adipic acid (MacGillavry, *Rec. Trav. Chim.*, 1941, **60**, 605).

In the present paper the parameters for β-succinic acid (the crystal modification which is stable at normal temperatures) are re-examined and an attempt is made to determine whether bond-length variations exist in the saturated carbon chain. Our results (Fig. 3) fully confirm the findings of Verweel and MacGillavry (*loc. cit.*). Our measurements indicate a slightly greater contraction in the central bond, but it is probable that final conclusions regarding this and other details of the fine structure will only be reached after making a full three-dimensional analysis of all the available intensity data. The present two-dimensional refinement of the parameters is a necessary foundation for this more comprehensive approach. It is also valuable in giving results which are strictly comparable to those obtained for the higher members of the series (Parts V and VI) for which the two-dimensional approach is the only one feasible at present. If certain regularities are detected in the fine structure for all the members in such a series of related compounds, then it may be possible to attach some significance to the results even although the individual observations are near to the limit of possible experimental error.

Crystal Data.—β-Succinic acid, $C_4H_6O_4$; M, 118·1; m. p. 185°; d, calc. 1·561, found 1·550. Monoclinic prismatic, $a = 5·10 \pm 0·01$, $b = 8·88 \pm 0·03$, $c = 7·61 \pm 0·02$ A., $\beta = 133·6° \pm 0·3°$. Absent spectra, ($h0l$) when h is odd, ($0k0$) when k is odd. Space group C_{2h}^5 ($P2_1/a$). Two molecules per unit cell. Molecular symmetry, centre. Volume of the unit cell, 249·6 A.^{3}. Absorption coefficient for X-rays ($\lambda = 1·54$ A.) $\mu = 14·25$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 124.

Crystallisation from water produces needles elongated in the direction of the c axis, but these are generally too thin to be of use in X-ray work. Slow crystallisation from ethyl acetate produces crystals with a tendency to elongation along the a axis which are suitable for X-ray work. Crystals so obtained are extremely brittle and difficult to cut without causing distortion. There is also a very marked fibre cleavage in the direction of the c axis. Faces most commonly developed are (001), (010), (111), (110), and (011).

FIG. 1.



Normal projection of succinic acid structure along a *axis. Contour scale : one electron per* A.^{2} *per line, one-electron line dotted.*

Further goniometric and optical data are given by Groth (" Chemische Krystallographie," 1919, **3**, 262) and the crystal structure has been investigated by Yardley (*Proc. Roy. Soc.*, 1924, *A*, **105**, 451) and Dupré la Tour (*Compt. rend.*, 1930, **191**, 1348; 1931, **193**, 180; *Ann. Physique*, 1932, **18**, 199), who determined the lattice constants and space group in reasonable agreement with our present work.

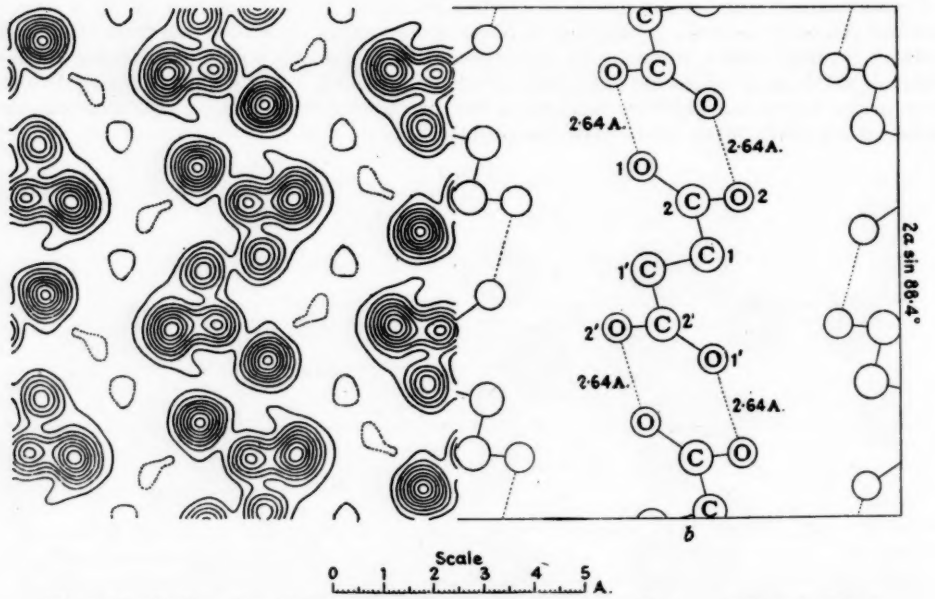
Analysis of the Structure.—A very full investigation of the structure has been made by Verweel and MacGillavry (*locc. cit.*) based on the intensities of the reflections from the three axial zones. Projections of the structure were made along the a and b crystal axes by the double Fourier series method, and from these results the atomic co-ordinates were determined. The resolution obtained in the a axis projection was good, but rather poor in the b axis projection owing to the close approach of certain pairs of atoms (see Fig. 4, this paper). Nevertheless, their final results are in very good agreement with those we have now obtained.

Starting with the co-ordinates of Verweel and MacGillavry, we have attempted to refine the structure further by the Fourier series method, with the inclusion of a larger number of reflecting planes and the preparation of new projection along the [101] axis which gives much better resolution of the atoms than can be obtained from the b axis projection. From these results we have obtained slight shifts in some of the atomic positions, necessitating change of sign for a few

reflections. These changes have been incorporated in our final syntheses which are shown as normal projections along the *a* axis and the [101] axis in Figs. 1 and 2.

The two projection axes are almost at right angles (88·4°) and it will be seen that in each projection all the atoms are separately resolved. All three co-ordinates for each atom may thus

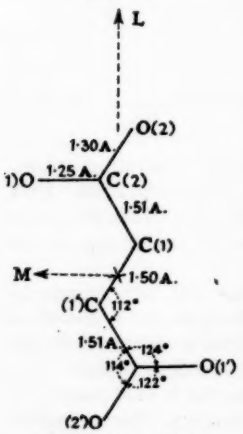
FIG. 2.



Normal projection of succinic acid structure along [101] *axis. Contour scale as in Fig.* 1.

be estimated with considerable accuracy. The positions which we have finally assigned to the centres of the atoms in the *a* axis projection are indicated by small crosses in Fig. 5, where the origin and co-ordinate network are also shown. A close examination of the contour levels in the *a* axis projection (Figs. 1 and 5) shows small peaks at the two-electron level which occur approximately where the hydrogen atoms of the CH_2 groups should appear, a normal tetrahedral distribution of the valency bonds about the carbon atoms being assumed. It is likely that these peaks are actually due to the hydrogen atoms, but confirmation by three-dimensional synthesis is awaited, and in the meantime no attempt has been made to include a hydrogen contribution in the calculation of the intensities. For the higher members of this series the hydrogen contribution to the total scattering becomes much more important, and the matter is further discussed in Part VI.

FIG. 3.



Dimensions of the succinic acid molecule.

Orientation, Co-ordinates, and Dimensions.—We choose as principal molecular axis *L* the line passing through the mid points of the three carbon–carbon bonds in the molecule (Fig. 3). The four carbon atoms in the molecule lie in one plane and so the second molecular axis *M* is chosen to lie in this plane at right angles to *L*. The third axis *N* is perpendicular to *L* and *M*. The orientation of the molecule in the crystal is then given by the angles in Table I, where χ, ψ, and ω are the angles which the molecular axes make with the *a*, *b*, and *c'* crystal axes, *c'* being chosen perpendicular to *a* and *b*.

The observed co-ordinates of the atoms in the asymmetric crystal unit (half the molecule) are listed in Table II, referred to the crystallographic axes. The co-ordinates of all the other atoms in the unit cell may be obtained from these by the appropriate symmetry operations, *viz.*, x, y, z; $-x, -y, -z$; $\frac{1}{2}+x, \frac{1}{2}-y, z$; $\frac{1}{2}-x, \frac{1}{2}+y, -z$. The co-ordinates referred to the molecular axes *L*, *M*, *N* are listed in Table III.

From the co-ordinates it is easy to deduce the bond lengths and valency angles. These are shown diagramatically in Fig. 3, and the figures are collected and compared with previous findings in Table IV. The agreement is on the whole extremely good, although we find a somewhat larger contraction in the length of the central bond, C(1′)–C(1). We believe this contraction to be significant, and it is confirmed by our work on the higher members of this series. The situation of the central carbon–carbon bond in succinic acid is clearly analogous to that of the central bond in dibenzyl and to the bond in geranylamine hydrochloride situated centrally between the ethylene linkages. In both these cases a notable contraction from the normal carbon–carbon single-bond length of 1·54 A. has been observed (Jeffrey, *Proc. Roy. Soc.*, 1947, *A*, **188**, 222; 1945, *A*, **183**, 388; Cox and Cruickshank, *Acta Cryst.*, 1948, **1**, 92).

TABLE I.

Orientation of the molecule in the crystal.

$\chi_L = 56{\cdot}0°$, $\cos\chi_L = 0{\cdot}5590$	$\chi_M = 60{\cdot}4°$, $\cos\chi_M = 0{\cdot}4944$	$\chi_N = 48{\cdot}2°$, $\cos\chi_N = 0{\cdot}6667$
$\psi_L = 68{\cdot}5°$, $\cos\psi_L = 0{\cdot}3670$	$\psi_M = 150{\cdot}2°$, $\cos\psi_M = -0{\cdot}8674$	$\psi_N = 70{\cdot}3°$, $\cos\psi_N = 0{\cdot}3370$
$\omega_L = 42{\cdot}0°$, $\cos\omega_L = 0{\cdot}7437$	$\omega_M = 86{\cdot}8°$, $\cos\omega_M = 0{\cdot}0563$	$\omega_N = 131{\cdot}7°$, $\cos\omega_N = -0{\cdot}6648$

TABLE II.

Observed co-ordinates. (*Centre of symmetry as origin.*)

x, y, z are referred to the monoclinic crystal axes, a, b, c; x', y, z' are orthogonal co-ordinates referred to the a and b crystal axes and their perpendicular c'.

Atom (cf. Fig. 3).	x, A.	y, A.	z, A.	x', A.	z', A.	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.
C(1)	0·276	0·592	0·602	0·140	0·436	19·5°	24·0°	28·5°
C(2)	0·099	0·326	1·966	1·257	1·432	7·0	13·2	93·0
O(1)	−0·602	−0·703	1·976	1·965	1·431	−42·5	−28·5	93·5
O(2)	0·864	1·233	2·234	1·367	2·342	61·0	50·0	153·0

TABLE III.

Co-ordinates referred to the molecular axes L, M, *and* N. (*Origin at centre of symmetry.*)

Atom.	L, A.	M, A.	N, A.	Atom.	L, A.	M, A.	N, A.
C(1)	0·620	−0·420	0·000	O(1)	1·904	1·662	0·122
C(2)	1·880	0·419	0·000	O(2)	2·959	−0·261	−0·230

TABLE IV.

Molecular dimensions.

	Present work.	Previous work.*		Present work.	Previous work.*
C(1′)–C(1)	1·50 ± 0·02 A.	1·52 A.	C(1′)–C(1)–C(2)	112°	112°
C(1)–C(2)	1·51 ,,	1·51	C(1)–C(2)–O(1)	124	125
C(2)–O(1)	1·25 ,,	1·28	C(1)–C(2)–O(2)	114	112
C(2)–O(2)	1·30 ,,	1·31	O(1)–C(2)–O(2)	122	123

* Verweel and MacGillavry, *locc. cit.*

TABLE V.

Intermolecular distances (A).*

O(1*A*) . . . O(2′*C*) = 2·64 ± 0·04	O(1*A*) . . . O(1′*D*) = 3·42 ± 0·04
O(2*A*) . . . O(1′*C*) = 2·64 ,,	O(2*A*) . . . C(1*B*) = 3·49 ,,
O(2′*C*) . . . O(1*B*) = 3·11 ,,	O(2′*C*) . . . C(1*D*) = 3·52 ,,
O(1′*C*) . . . O(2*B*) = 3·11 ,,	O(1*A*) . . . C(1′*D*) = 3·53 ,,
O(2*A*) . . . O(2*B*) = 3·23 ,,	O(1*A*) . . . C(1*D*) = 3·66 ,,

* A = standard molecule; B = reflected molecule; C = molecule one translation along c axis.

All the carbon atoms in the molecule are necessarily coplanar, and this plane passes through the centre of symmetry in the middle of the molecule. The planes of the carboxyl groups, however, are rotated through about 9° about the axis C(1)–C(2) with respect to the plane containing the carbon atoms. The plane of the carboxyl group also passes through the centre of symmetry which is situated between the ends of adjoining molecules in the c axis direction. It follows, therefore, that adjoining carboxyl groups, which are linked by hydrogen bridges (see Fig. 4), are coplanar.

Intermolecular Distances.—The more important intermolecular distances are indicated by dotted lines in Fig. 4, which represents a projection of the structure along the b axis on the (010) plane. Some of these intermolecular approaches are also marked in the line drawings which

accompany the contour maps in Figs. 1 and 2. The closest approach between molecules occurs in the hydrogen bridges of length 2·64 A. which connect the oxygen atoms of adjacent carboxyl groups along the *c* axis. Certain other oxygen–oxygen distances, particularly a pair at 3·11 A., are also shorter than is usual in the acids of this series, and this leads to an exceptionally compact grouping of the succinic acid molecules. The shortest carbon–oxygen distance is 3·49 A. between molecules *A* and *B*. The figures are collected in Table V.

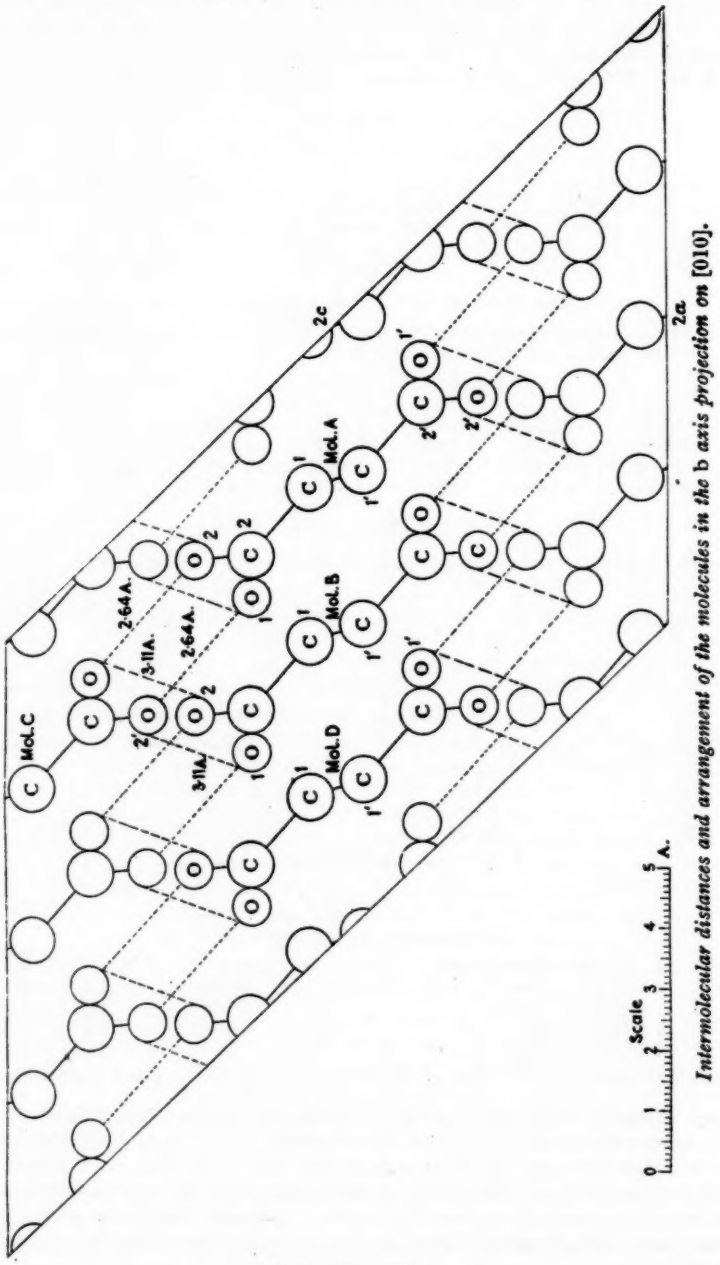


FIG. 4. *Intermolecular distances and arrangement of the molecules in the* b *axis projection on* [010].

EXPERIMENTAL.

X-*Ray Measurements.*—Copper *K*-α radiation ($\lambda = 1{\cdot}54$ A.) was used throughout this work, and rotation, oscillation, and moving-film photographs of all the principal zones were taken. The intensities were estimated visually, with the help of the multiple-film technique (Robertson, *J. Sci. Instr.*, 1943, **20**,

TABLE VI.

Measured and calculated values of the structure factor.

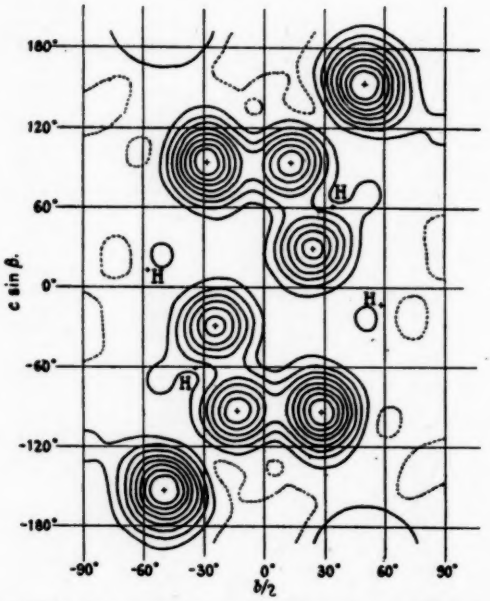
hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54).	F, meas.	F, calc.
020	0·173	24·0	+34·0	017	0·983	<0·5	+ 0·0
040	0·346	15·5	−16·0	027	0·995	<0·5	− 0·0
060	0·519	7·5	− 9·0				
080	0·692	4·0	− 3·5	$20\bar{2}$	0·299	17·5	−18·0
0,10,0	0·865	3·5	− 2·5	$40\bar{4}$	0·598	7·0	+ 8·0
				$60\bar{6}$	0·886	3·5	− 2·5
001	0·140	6·0	−10·5				
002	0·280	10·5	−13·0	$11\bar{1}$	0·173	2·0	− 0·0
003	0·419	<1·0	+ 2·5	$21\bar{2}$	0·311	8·0	+ 9·5
004	0·559	9·0	+ 9·0	$31\bar{3}$	0·459	10·0	+12·5
005	0·699	2·0	− 1·5	$41\bar{4}$	0·606	2·0	+ 2·0
006	0·838	9·5	− 7·5	$51\bar{5}$	0·755	6·0	+ 4·0
007	0·978	0·5	+ 1·5	$61\bar{6}$	0·889	<1·0	− 0·5
011	0·165	5·0	+ 4·0				
021	0·223	10·0	+10·0	$12\bar{1}$	0·229	17·5	+17·0
031	0·295	1·5	− 1·0	$22\bar{2}$	0·347	1·0	+ 1·0
041	0·373	10·0	+12·0	$32\bar{3}$	0·482	16·5	−18·5
051	0·455	3·0	− 1·5	$42\bar{4}$	0·624	2·5	+ 1·0
061	0·537	6·5	− 8·5	$52\bar{5}$	0·770	7·5	+ 7·0
071	0·622	7·0	+ 7·0	$62\bar{6}$	0·903	1·5	− 0·5
081	0·706	6·5	− 5·0				
091	0·791	6·5	+ 5·5	$13\bar{1}$	0·299	2·5	+ 3·5
0,10,1	0·876	<1·0	+ 1·0	$23\bar{2}$	0·396	15·5	+17·5
0,11,1	0·961	1·5	+ 1·0	$33\bar{3}$	0·518	<1·5	− 0·0
				$43\bar{4}$	0·653	2·0	+ 2·5
012	0·292	7·0	− 6·5	$53\bar{5}$	0·793	3·0	+ 1·5
022	0·329	14·5	−16·0	$63\bar{6}$	0·924	<1·0	− 0·5
032	0·381	4·5	+ 3·0				
042	0·445	9·0	− 7·0	$14\bar{1}$	0·378	7·0	− 5·0
052	0·514	11·0	+12·5	$24\bar{2}$	0·457	4·5	+ 6·0
062	0·590	6·5	+ 6·5	$34\bar{3}$	0·566	4·0	− 4·0
072	0·667	<1·5	+ 1·0	$44\bar{4}$	0·689	<1·5	− 1·0
082	0·746	4·0	+ 3·5	$54\bar{5}$	0·744	4·5	+ 4·5
092	0·828	4·0	− 3·0	$64\bar{6}$	0·952	<1·0	+ 1·0
0,10,2	0·909	1·0	− 0·5				
0,11,2	0·992	<0·5	− 0·5	$15\bar{1}$	0·457	2·5	+ 4·5
013	0·429	15·5	+17·5	$25\bar{2}$	0·524	9·5	+ 9·0
023	0·454	2·0	+ 3·0	$35\bar{3}$	0·622	4·5	− 0·0
033	0·494	15·5	+18·0	$45\bar{4}$	0·738	<1·5	+ 0·5
043	0·544	2·0	+ 1·0	$55\bar{5}$	0·865	2·0	− 1·5
053	0·602	2·5	− 2·5	$65\bar{6}$	0·985	<0·5	+ 0·5
063	0·667	1·5	− 1·5				
073	0·737	4·0	− 3·5	$16\bar{1}$	0·541	2·0	− 1·5
083	0·809	1·5	− 1·0	$26\bar{2}$	0·599	7·0	− 8·5
093	0·885	4·0	− 1·5	$36\bar{3}$	0·686	1·5	+ 1·0
0,10,3	0·961	<1·0	+ 0·0	$46\bar{4}$	0·792	4·0	+ 6·0
				$56\bar{5}$	0·914	3·0	+ 0·5
014	0·565	4·5	− 5·0				
024	0·586	8·0	+ 9·0	$17\bar{1}$	0·624	<1·5	− 0·0
034	0·616	1·5	− 0·0	$27\bar{2}$	0·676	<1·5	− 1·0
044	0·658	3·0	+ 1·5	$37\bar{3}$	0·753	4·0	− 3·5
054	0·707	8·0	+ 6·0	$47\bar{4}$	0·850	<1·5	− 0·5
064	0·763	3·5	− 2·5	$57\bar{5}$	0·964	2·5	− 2·0
074	0·824	2·5	+ 1·0				
084	0·889	1·5	− 1·5	$18\bar{1}$	0·707	9·5	+ 7·5
094	0·958	2·0	− 1·5	$28\bar{2}$	0·753	6·0	− 3·5
				$38\bar{3}$	0·825	3·0	− 2·0
015	0·704	2·0	+ 1·5	$48\bar{4}$	0·915	1·0	+ 1·0
025	0·719	4·0	− 3·5				
035	0·745	2·0	+ 0·5	$19\bar{1}$	0·792	2·0	− 1·0
045	0·780	2·5	− 2·0	$29\bar{2}$	0·835	3·0	− 2·5
055	0·822	<1·0	− 1·0	$39\bar{3}$	0·899	2·0	− 1·0
065	0·872	4·0	+ 2·0	494	0·982	0·5	− 0·5
075	0·924	2·5	+ 1·5				
085	0·984	2·0	+ 1·5	1,10,$\bar{1}$	0·879	4·5	+ 3·0
				2,10,$\bar{2}$	0·915	1·5	+ 1·5
016	0·844	<1·0	− 0·0	3,10,$\bar{3}$	0·974	2·0	− 0·5
026	0·856	5·0	− 3·0				
036	0·879	1·0	+ 0·5	1,11,$\bar{1}$	0·962	1·0	− 0·5
046	0·907	1·5	+ 1·5				
056	0·943	<1·0	+ 0·5				
066	0·987	1·0	+ 1·0				

175) over a range of about 1500 to 1. Only moving-film photographs were employed for the intensity work. The usual correction factors were applied, and the observed structure factors are collected in Table VI.

The crystal specimens used for these measurements for the (0*kl*) zone had cross-sections normal to the *a* axis of 0·09 mm. × 0·11 mm. and 0·45 mm × 0·52 mm. For the (*hk*$\bar{h}$) zone the cross-section was 0·38 mm. × 0·42 mm. The specimens were completely immersed in the *X*-ray beam, and absorption corrections for different reflections in the same zone were not applied. Most of the specimens were characterised by a high degree of perfection of the crystal faces. To ensure that the crystals were of the true mosaic type some specimens were immersed in liquid air before use. The intensities from crystals so treated did not, however, appear to differ from those of other specimens. As will be noted from Table VI, intensities were recorded from nearly all the reflections possible for copper radiation in the two zones examined.

Fourier Analysis and Structure-factor Calculations.—For the projection along the *a* axis the electron density was computed by the usual series at 450 points on the asymmetric unit, the *b* axis being subdivided into 60 parts of 0·148 A. and *c* sin β into 30 parts of 0·184 A. The summations were carried out by three-figure methods (Robertson, *J. Sci. Instr.*, 1948, **25**, 28) and the results were plotted on a scale of 5 cm. per A. by graphical interpolation from the summation totals. The resulting contour map for the (0*kl*) zone, showing the positions finally assigned to the atom centres and the co-ordinate network, is given in Fig. 5. The projection along the [101] axis was computed similarly, in this case the summation intervals being $b/60 = 0{\cdot}148$ A., and $a \cos 1{\cdot}6°/30 = 0{\cdot}170$ A.

FIG. 5.



Contour map for a axis projection showing positions assigned to atoms. The approximate positions expected for the hydrogen atoms of the CH_2 *groups, assuming normal bond lengths and angles, are indicated by the letters* H.

The structure factors calculated from the final co-ordinates are listed in Table VI under " F, calc." A single composite atomic scattering curve was used, the *f*-values being as follows :

$\sin\theta/\lambda$ (λ = 1·54).....	0·0	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9
f_e	100	75	60	49	38	29	19	13	8·4	4·7

On this basis the oxygen contributions relative to the carbon contributions were weighted in the ratio of 1·5 to 1·0. This treatment is not very satisfactory, especially for a molecule with such a high proportion of oxygen as succinic acid, but it is sufficient for the present purpose.

The discrepancies between the measured and calculated structure factors, expressed as

$$\frac{\Sigma(|F,\text{obs.}| - |F,\text{calc.}|)}{\Sigma|F,\text{obs.}|} \times 100$$

are 22·5% for the (0*kl*) zone and 21·7% for the (*hk*$\bar{h}$) zone, giving an overall discrepancy of 22·0%. It is likely that these figures could be greatly improved by the use of separate *f* curves for oxygen and carbon, but as they stand they show that a considerable refinement of the previous work (Verweel and MacGillavry, *loc. cit.*) has been attained.

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210. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part V. Adipic Acid.*

By J. D. Morrison and J. Monteath Robertson.

The crystal structure of adipic acid has been further refined by means of two projections and the use of very complete Fourier series. The measurements indicate an alternation of long and slightly shorter bonds over the entire length of the six-membered carbon chain, although these variations are barely greater than the possible experimental error. The arrangement of the molecules in the crystal is discussed and it is shown that, in addition to the end-to-end hydrogen bonding between the carboxyl groups of adjoining molecules, there is an unusually close lateral approach (3·3 A.) between an oxygen atom of one molecule and the second carbon atom in the chain of another molecule.

A quantitative determination of the crystal structure of adipic acid has recently been carried out by MacGillavry (*Rec. Trav. chim.*, 1941, **60**, 605) with results which show interesting contractions in the carbon–carbon bond lengths in the saturated chain, the mean value being about 1·51 A. as compared with the accepted normal value of 1·54 A. In the present paper we have attempted a further refinement of this structure based on the use of more complete Fourier series. Our results are in excellent general agreement with those of MacGillavry, but we obtain a different distribution of bond length variations in the chain. We believe the pattern of variations now obtained is significant, and it will be further discussed in a later paper in connection with a theory of the alternating effects in homologous series of aliphatic compounds.

Crystal Data.—Adipic acid, $C_6H_{10}O_4$; M, 146·1; m. p. 153°; d, calc. 1·359, found 1·345. Monoclinic prismatic, $a = 10{\cdot}07 \pm 0{\cdot}03$, $b = 5{\cdot}16 \pm 0{\cdot}01$, $c = 10{\cdot}03 \pm 0{\cdot}03$ A., $\beta = 137{\cdot}1° \pm 0{\cdot}2°$. Absent spectra, $(h0l)$ when h is odd, $(0k0)$ when k is odd. Space group $C_{2h}^5(P2_1/a)$. Two molecules per unit cell. Molecular symmetry, centre. Volume of the unit cell, 355 A.^{3}. Absorption coefficient for X-rays ($\lambda = 1{\cdot}54$ A.) $\mu = 12{\cdot}0$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 156.

Well-formed crystals were obtained by slow evaporation of solutions in ethyl acetate. The crystals were frequently elongated in the direction of the b axis, the (001) and (100) faces being generally well developed; (110) and (011) also appear. There is pronounced cleavage on (010).

Further crystal data are given by Groth ("Chemische Krystallographie", 1919, **3**, 465), and Caspari (*J.*, 1928, 3235) has determined the lattice constants and space group in agreement with our data.

Analysis of the Structure.—The cell dimensions in adipic acid are considerably different from those of succinic acid (Part IV, preceding paper). In both cases the molecules are arranged end-to-end along the direction of the c axis, but the lateral arrangement of the chains is different in the two structures.

The adipic acid structure has been determined in detail by MacGillavry (*loc. cit.*) and it is not necessary to describe it again here. We are concerned with a further refinement of the parameters determined by MacGillavry. This was carried out by several successive Fourier syntheses giving projections of the structure along the b axis and along the [101] axis. In the final b axis projection 80 out of a possible 91 reflections (to the limit of copper radiation) were included, and in the [101] axis projection 58 out of a possible 63 reflections. These figures compare with totals of 58 and 35 terms in the corresponding series employed by MacGillavry.

Our final electron-density maps are shown in Figs. 1 and 2, from which it is clear that good resolution of most of the atoms is obtained. In the b axis projection (Fig. 1) one of the carboxyl oxygen atoms and one of the carbon atoms are obscured, and their positions cannot be determined with quite the same certainty as the others. Bulges on the one-electron line (dotted) near the central pair of carbon atoms in Fig. 1 appear to indicate the presence of hydrogen atoms, but this matter has not been further investigated in the present structure.

Orientation, Co-ordinates, and Dimensions.—The molecular axes are chosen as for succinic acid (Part IV), L passing through the mid points of the three central carbon–carbon bonds, and M lying in the plane of the four central carbon atoms (Fig. 3); N is perpendicular to L and M. The angles which these axes make with the a and b crystal axes and their perpendicular (c') are given in Table I.

Table I.

Orientation of the molecule in the crystal.

$\chi_L = 48{\cdot}5°$, $\cos\chi_L = 0{\cdot}6633$	$\chi_M = 61{\cdot}0°$, $\cos\chi_M = 0{\cdot}4854$	$\chi_N = 55{\cdot}3°$, $\cos\chi_N = 0{\cdot}5699$
$\psi_L = 104{\cdot}6°$, $\cos\psi_L = -0{\cdot}2517$	$\psi_M = 30{\cdot}5°$, $\cos\psi_M = 0{\cdot}8616$	$\psi_N = 116{\cdot}2°$, $\cos\psi_N = -0{\cdot}4411$
$\omega_L = 45{\cdot}2°$, $\cos\omega_L = 0{\cdot}7047$	$\omega_M = 98{\cdot}6°$, $\cos\omega_M = -0{\cdot}1489$	$\omega_N = 133{\cdot}9°$, $\cos\omega_N = -0{\cdot}6936$

The estimated co-ordinates of the atoms in the asymmetric crystal unit (half the molecule) are listed in Table II, referred to the crystal axes. The co-ordinates referred to the molecular axes, *L*, *M*, and *N*, as defined above, are given in Table III.

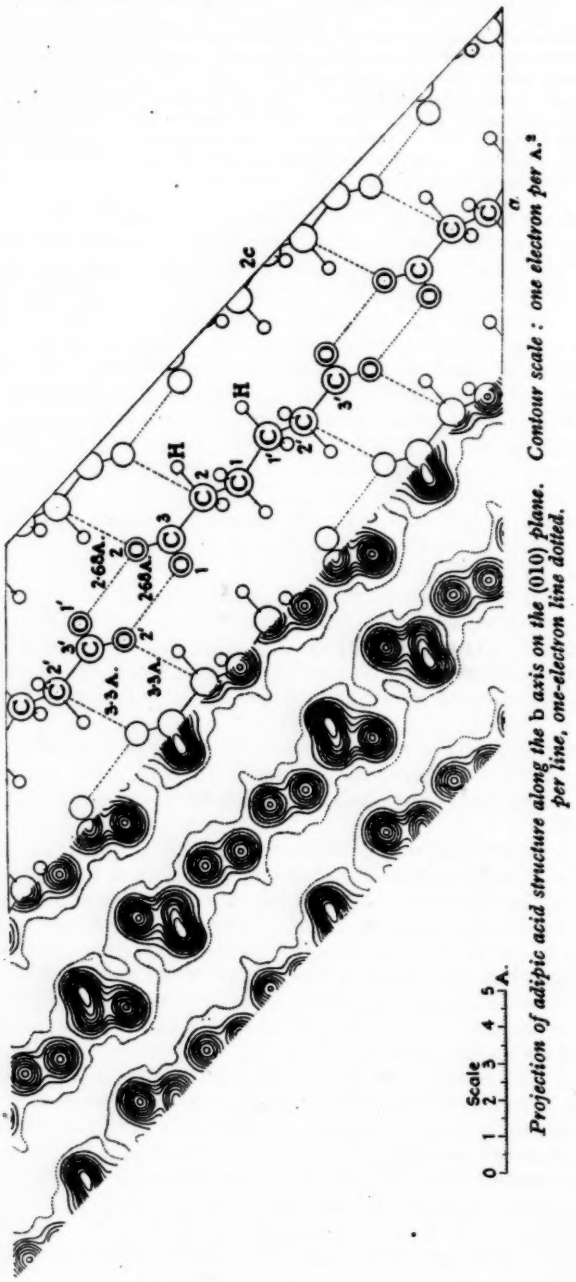


FIG. 1.

Projection of adipic acid structure along the b *axis on the (010) plane. Contour scale: one electron per* A.^{3} *per line, one-electron line dotted.*

The bond lengths and valency angles deduced from the co-ordinates are shown in Fig. 3. The figures are collected and compared with previous work in Table IV. The agreement on the whole is good, the greatest divergence being in the carboxyl group where the distances are in any case extremely difficult to determine with precision.

Our measurements indicate a distinct alternation of long and slightly shorter bonds over the

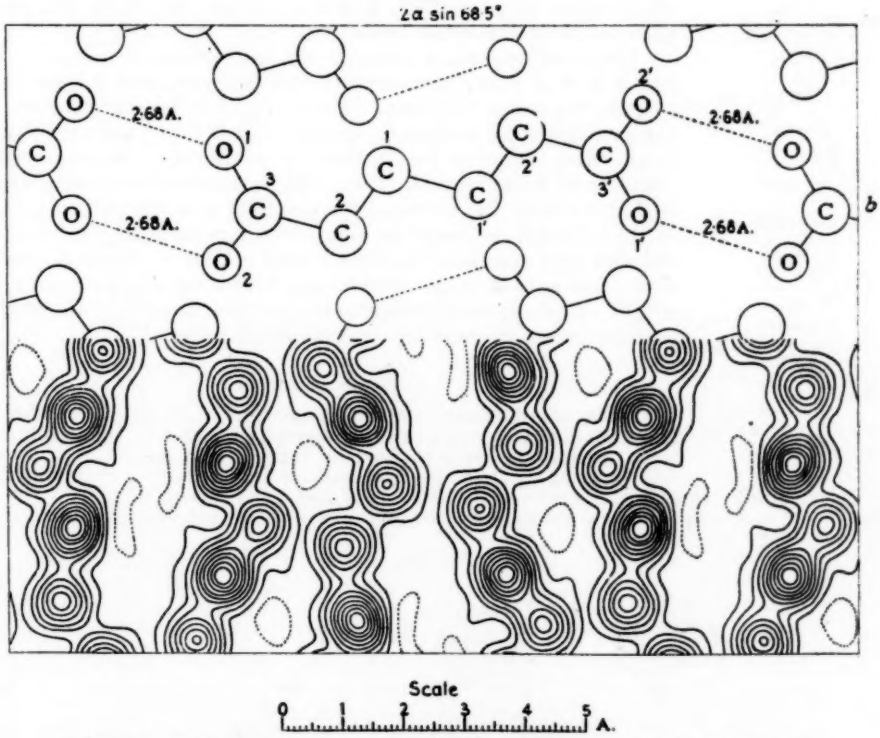
TABLE II.

Co-ordinates. Centre of symmetry as origin.

x, *y*, *z* refer to monoclinic crystal axes; *x'*, *y*, *z'* refer to orthogonal axes *a*, *b*, and *c'*.

Atom (cf. Fig. 3).	*x*, A.	*y*, A.	*z*, A.	*x'*, A.	*z'*, A.	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.
C(1)	−0·215	0·206	0·573	0·634	0·390	− 7·7°	14·3°	21·5°
C(2)	0·453	−0·838	2·027	1·032	1·380	16·0	−58·5	72·6
C(3)	0·269	−0·448	3·355	2·188	2·284	9·6	−31·5	120·0
O(1)	−0·715	0·540	2·945	2·872	2·006	−25·7	37·5	105·5
O(2)	1·025	−1·296	4·730	2·438	3·220	36·7	−90·5	170·0

FIG. 2.



Projection of adipic acid structure along [101] *axis. Contour scale as in Fig.* 1.

TABLE III.

Co-ordinates referred to molecular axes L, M, *and* N. (*Origin at centre of symmetry.*)

Atom.	*L*, A.	*M*, A.	*N*, A.	Atom.	*L*, A.	*M*, A.	*N*, A.
C(1)	0·644	0·427	0·000	O(1)	3·183	1·561	0·008
C(2)	1·868	−0·427	0·000	O(2)	4·213	−0·414	−0·272
C(3)	3·175	0·336	−0·138				

TABLE IV.

Molecular dimensions.

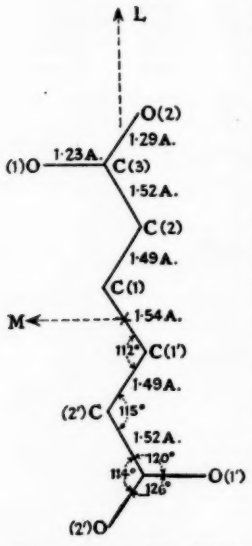
Present work.	Previous work.*	Present work.	Previous work.*
C(1')–C(1) = 1·54 ± 0·02 A.	1·51 A.	C(1')–C(1)–C(2) = 112°	112°
C(1)–C(2) = 1·49 ,,	1·52	C(1)–C(2)–C(3) = 115	114
C(2)–C(3) = 1·52 ± 0·03	1·49	C(2)–C(3)–O(1) = 120	122
C(3)–O(1) = 1·23 ± 0·04	1·28	C(2)–C(3)–O(2) = 114	114
C(3)–O(2) = 1·29 ,,	1·38	O(1)–C(3)–O(2) = 126	124

* MacGillavry (*loc. cit.*).

entire length of the six-carbon saturated chain. The variations are not much greater than the possible experimental error, but they are confirmed to some extent by our other measurements in this series.

With regard to the geometry of the molecule, the four central carbon atoms are necessarily coplanar with the centre of symmetry. The terminal carbon atom, however, with the oxygens of the carboxyl group, lie on another plane which is tilted by about 6° to the plane of the carbon chain. This plane through the carboxyl group includes the centre of symmetry between adjacent molecules along the *c* axis and passes through the carboxyl group of the next molecule.

FIG. 3.



Dimensions of the ddipic acid molecule.

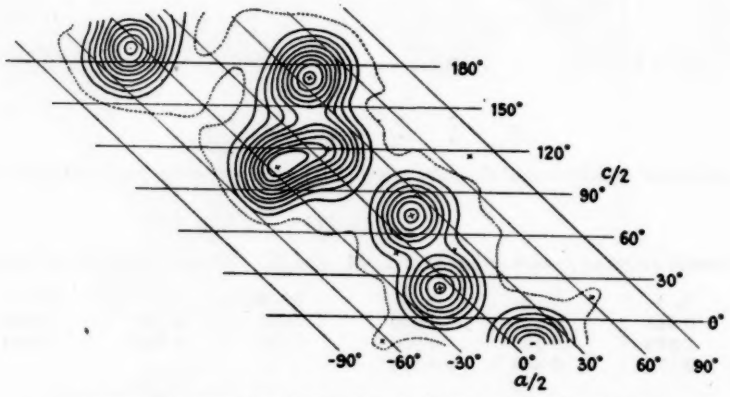
Intermolecular Distances.—The significant intermolecular approach distances are marked by dotted lines in the drawings which accompany the contour maps in Figs. 1 and 2. These and other distances less than 4 A. are collected in Table V.

The most important linkages are the hydrogen bridges of length about 2·68 A. which connect the carboxyl groups of adjoining molecules in the *c* axis direction. These appear to be slightly longer than the corresponding bridges in succinic acid (2·64 A.) and very distinctly longer than some of the bridges in oxalic acid dihydrate (Part I, Dunitz and Robertson, *J.*, 1947, 142). Another interesting approach is that between the carboxyl oxygen O(2) and the carbon atom C(2) of the reflected molecule one translation further along the *c* axis. The order of this approach distance would appear to indicate some very weak and unusual type of hydrogen bridge involving a carbon atom. All the other approach distances are greater than 3·6 A. and would not therefore seem to have any special significance.

EXPERIMENTAL.

X-Ray Measurements.—All the *X*-ray work was carried out with copper *K*-α radiation ($\lambda = 1{\cdot}54$ A.) and photographic methods. The cell dimensions, space group, etc., were checked by rotation and oscillation photographs, while moving-film methods were employed exclusively for the intensity work. The principal crystal specimen used for the (*h*0*l*) zone had cross-section normal to the *b* axis 0·77 mm × 0·43 mm. Approximate absorption corrections were applied, but were found to make little

FIG. 4.



Asymmetric crystal unit, showing positions assigned to atoms.

TABLE V.

Intermolecular distances (A.).*

O(1*A*) . . . O(2*C*)	= 2·68 ± 0·05	O(2*C*) . . . O(2*B*)	= 3·66 ± 0·05
O(2*B*) . . . C(2*C*)	= 3·29 ,,	C(1*B*) . . . O(1*A*)	= 3·72 ,,
O(2*A*) . . . O(2*C*)	= 3·60 ,,	C(2*B*) . . . O(2*C*)	= 3·94 ,,
C(1'*B*) . . . O(1*A*)	= 3·62 ,,	C(2*B*) . . . O(1*A*)	= 3·98 ,,

A = standard molecule; *B* = reflected molecule; *C* = molecule one translation along *c* axis.

TABLE VI.

Measured and calculated values of the structure factor.

hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54).	F, meas.	F, calc.
200	0·212	67·5	+62·0	801	0·979	1·5	− 1·5
400	0·423	6·0	+ 5·0	80$\bar{1}$	0·813	3·0	+ 3·5
600	0·634	1·5	− 4·5	80$\bar{2}$	0·740	1·5	+ 4·5
800	0·845	<1·0	+ 1·5	80$\bar{3}$	0·683	6·0	−10·0
				80$\bar{4}$	0·639	<1·5	+ 0·5
001	0·113	20·0	−22·0	80$\bar{5}$	0·611	11·0	−11·5
002	0·225	7·0	− 7·0	80$\bar{6}$	0·608	2·5	+ 3·0
003	0·337	6·5	+ 5·5	80$\bar{7}$	0·621	7·0	− 8·0
004	0·449	17·0	+16·0	80$\bar{8}$	0·656	4·5	+ 4·0
005	0·562	13·0	−13·0	80$\bar{9}$	0·710	8·5	− 7·0
006	0·674	6·0	+ 5·5	8,0,$\bar{1}$0	0·790	<1·0	+ 0·0
007	0·787	4·0	− 3·0	8,0,$\bar{1}$1	0·850	1·5	− 1·0
008	0·899	4·5	− 3·5	8,0,$\bar{1}$2	0·935	7·0	+ 4·0
207	0·965	2·0	− 2·5	10,0,$\bar{2}$	0·960	1·0	+ 0·5
206	0·855	1·0	+ 1·0	10,0,$\bar{3}$	0·894	1·5	− 4·0
205	0·743	2·5	− 4·0	10,0,$\bar{4}$	0·836	<1·0	+ 2·5
204	0·633	11·5	+13·5	10,0,$\bar{5}$	0·796	8·0	− 6·5
203	0·525	3·0	+ 1·0	10,0,$\bar{6}$	0·770	4·0	− 4·0
202	0·418	11·0	− 8·0	10,0,$\bar{7}$	0·758	4·0	+ 2·0
201	0·317	3·0	+ 2·0	10,0,$\bar{8}$	0·763	1·0	+ 2·0
20$\bar{1}$	0·160	2·0	− 3·0	10,0,$\bar{9}$	0·784	5·0	− 4·0
20$\bar{2}$	0·164	12·5	−15·0	10,0,$\bar{1}$0	0·821	2·5	− 2·0
20$\bar{3}$	0·233	25·5	+28·5	10,0,$\bar{1}$1	0·870	4·5	+ 3·0
20$\bar{4}$	0·329	21·0	−19·0	10,0,12	0·935	3·0	+ 1·0
20$\bar{5}$	0·434	6·0	− 7·0				
20$\bar{6}$	0·539	8·0	+ 7·0	12,0,$\bar{3}$	0·960	2·5	− 4·0
207	0·646	<1·5	+ 0·5	12,0,7	0·930	3·5	+ 3·5
208	0·756	15·5	−14·5	12,0,$\bar{8}$	0·915	1·5	− 1·0
209	0·868	2·5	+ 2·5	12,0,$\bar{9}$	0·914	1·0	− 0·5
2,0,$\bar{1}$0	0·980	<0·5	+ 0·5	12,0,$\bar{1}$0	0·925	<1·0	− 1·0
				12,0,$\bar{1}$1	0·960	2·5	+ 2·5
405	0·944	1·0	+ 1·5	12,0,$\bar{1}$2	0·988	<0·5	− 1·0
404	0·838	2·5	+ 2·5				
403	0·735	6·0	+ 4·0	020	0·299	5·5	− 3·5
402	0·631	3·5	− 5·0	040	0·597	2·0	− 2·5
401	0·538	11·0	+12·0	060	0·896	1·5	− 3·0
40$\bar{1}$	0·371	19·5	+19·5				
40$\bar{2}$	0·320	9·0	−11·0	11$\bar{1}$	0·171	3·0	+ 1·0
40$\bar{3}$	0·303	25·0	+26·5	12$\bar{1}$	0·310	3·5	+ 3·5
40$\bar{4}$	0·329	47·0	−46·0	13$\bar{1}$	0·457	4·0	+ 4·5
40$\bar{5}$	0·390	3·5	+ 3·5	14$\bar{1}$	0·606	4·0	− 4·0
40$\bar{6}$	0·468	7·0	+ 7·0	15$\bar{1}$	0·753	4·5	+ 4·5
407	0·556	3·5	− 2·0	16$\bar{1}$	0·903	1·0	− 0·0
408	0·655	22·5	−19·5				
409	0·758	4·0	+ 4·0	21$\bar{2}$	0·223	5·5	− 5·0
4,0,$\bar{1}$0	0·864	<1·0	− 0·0	22$\bar{2}$	0·342	4·5	+ 4·0
4,0,$\bar{1}$1	0·975	2·0	− 1·0	23$\bar{2}$	0·480	12·5	+14·0
				24$\bar{2}$	0·620	5·0	+ 8·0
603	0·948	2·5	+ 1·5	25$\bar{2}$	0·766	7·5	− 9·0
602	0·848	2·5	+ 0·5	26$\bar{2}$	0·913	0·5	+ 1·0
601	0·756	<1·5	+ 3·5				
60$\bar{1}$	0·590	11·5	+12·5	31$\bar{3}$	0·290	16·5	+16·5
60$\bar{2}$	0·525	2·0	+ 3·0	32$\bar{3}$	0·388	14·5	−16·0
60$\bar{3}$	0·478	1·5	− 2·0	33$\bar{3}$	0·513	2·0	+ 3·0
60$\bar{4}$	0·458	21·0	−22·5	34$\bar{3}$	0·647	7·0	− 7·0
60$\bar{5}$	0·463	5·5	− 6·0	35$\bar{3}$	0·788	5·0	− 5·5
60$\bar{6}$	0·495	8·5	+ 9·5	36$\bar{3}$	0·933	1·5	− 0·5
607	0·548	12·5	−11·5				
608	0·616	7·0	− 7·5	41$\bar{4}$	0·363	7·5	+ 4·5
609	0·695	3·5	− 2·0	42$\bar{4}$	0·446	9·0	+10·0
6,0,$\bar{1}$0	0·790	<1·0	+ 1·0	43$\bar{4}$	0·557	3·0	− 1·5
6,0,$\bar{1}$1	0·883	3·5	− 3·0	44$\bar{4}$	0·683	0·5	− 0·5
6,0,$\bar{1}$2	0·975	4·5	+ 4·0	45$\bar{4}$	0·816	1·0	+ 0·5
				46$\bar{4}$	0·958	<0·5	+ 1·5

TABLE VI.—*continued.*

hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.
51$\bar{5}$	0·439	9·0	− 7·0
52$\bar{5}$	0·504	1·5	− 0·0
53$\bar{5}$	0·609	3·0	− 4·5
54$\bar{5}$	0·726	2·5	+ 2·5
55$\bar{5}$	0·853	<0·5	+ 0·0
56$\bar{5}$	0·988	<0·5	− 1·0
61$\bar{6}$	0·516	1·5	− 1·0
62$\bar{6}$	0·578	7·0	− 6·5
63$\bar{6}$	0·667	14·0	−14·0
64$\bar{6}$	0·778	5·5	− 4·0
65$\bar{6}$	0·895	1·0	+ 2·0
71$\bar{7}$	0·596	6·0	− 5·5
72$\bar{7}$	0·650	8·0	+ 7·5
73$\bar{7}$	0·731	3·0	− 3·0
74$\bar{7}$	0·831	1·5	+ 1·5
75$\bar{7}$	0·944	<0·5	+ 1·0
81$\bar{8}$	0·675	5·5	+ 5·0
82$\bar{8}$	0·724	5·5	− 6·0
83$\bar{8}$	0·797	4·0	+ 4·5
84$\bar{8}$	0·890	1·0	+ 1·0
85$\bar{8}$	0·995	<1·0	− 0·5
91$\bar{9}$	0·759	3·0	− 2·0
92$\bar{9}$	0·800	3·0	− 3·0
93$\bar{9}$	0·867	0·5	+ 1·5
94$\bar{9}$	0·955	1·5	− 1·0
10,1,1$\bar{0}$	0·839	1·0	− 1·5
10,2,1$\bar{0}$	0·879	3·5	+ 2·0
10,3,1$\bar{0}$	0·940	5·5	+ 3·5
11,1,1$\bar{1}$	0·919	1·5	+ 1·5
11,2,1$\bar{1}$	0·955	<0·5	+ 0·0
110	0·184	60·5	+54·5
120	0·317	19·5	+13·5
130	0·461	7·5	+ 7·0
140	0·606	2·0	+ 2·0
150	0·754	4·0	− 4·5
160	0·902	<2·0	− 0·5
210	0·259	42·5	+39·5
220	0·366	6·0	+ 7·5
230	0·496	4·0	+ 1·5
240	0·634	5·0	− 4·5
250	0·775	2·5	+ 3·0
260	0·921	<1·5	− 1·5
310	0·350	19·5	+25·5
320	0·434	22·5	+24·5
330	0·549	<2·0	− 1·5
340	0·676	4·0	+ 3·5
350	0·810	3·0	− 1·5
360	0·950	<1·5	− 1·0
410	0·447	20·0	+25·5
420	0·516	9·0	+14·5
430	0·615	7·5	+ 6·5
440	0·731	4·5	− 3·5
450	0·857	<2·0	+ 1·0
460	0·991	<1·0	+ 1·0
510	0·548	4·5	+ 4·5
520	0·606	9·5	+14·0
530	0·692	<2·5	+ 2·0
540	0·796	2·0	+ 3·0
550	0·914	<1·5	+ 1·0
610	0·650	4·5	+ 3·5
620	0·699	4·5	+ 5·5
630	0·777	5·5	+ 7·0
640	0·870	<2·0	+ 0·0
650	0·978	<1·0	− 1·0
710	0·753	<2·5	− 1·0
720	0·796	5·0	+ 4·5
730	0·864	<2·0	+ 0·5
740	0·949	<1·5	+ 0·5
810	0·857	<2·0	− 0·5
820	0·896	<2·0	− 0·0
830	0·955	<1·5	+ 2·5
910	0·960	<1·0	− 0·5
920	0·995	<1·0	+ 0·5

difference save for one or two planes. For the strongest reflections a small crystal, cross-section 0·11 mm. × 0·16 mm., was used. For the ($hk\bar{h}$) zone a specimen of cross-section 0·47 mm. × 0·55 mm. was used, and for the ($hk0$) zone, one of 0·41 mm. × 0·58 mm. The multiple-film technique was used to correlate visual estimates of intensities over a total range of about 12,000 to 1, and the sets of intensities for the different zones were correlated by means of their common axial reflections. The structure factors were derived by the usual formulæ for mosaic-type crystals and the results are listed in Table VI. The absolute scale was derived by correlation with the F values calculated from the final co-ordinates.

Fourier Analysis.—In the projection along the *b* axis the electron density was computed at 900 points on the asymmetric unit, the axial subdivisions being $a/60 = 0{\cdot}168$ A. and $c/60 = 0{\cdot}167$ A. The usual three figure methods were employed. The positions finally assigned to the atoms in the asymmetric unit are shown in Fig. 4, which is superimposed on the co-ordinate net-work.

For the [101] axis projection the axial sub-divisions were $b/30 = 0{\cdot}172$ A., and $a \cos 21{\cdot}5°/60 = 0{\cdot}156$ A.

From the final co-ordinates the structure factors were recalculated, making use of the composite scattering curve given in Part IV. This curve was originally derived from the adipic acid work, and is not really very suitable for succinic acid. As before, the oxygen contributions were weighted relatively to the carbon contributions in the ratio 1·5 to 1·0. The results are shown in Table VI. The mean discrepancies between the calculated and observed structure factors, expressed in the usual manner (see Part IV), are 15·5% for the ($h0l$) zone, and 16·7% for the ($hk\bar{h}$) zone.

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211. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part VI. Sebacic Acid.*

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The crystal structure of sebacic acid has been fully determined by quantitative *X*-ray analysis, and is found to be similar to that of adipic acid. The finer details of the molecular structure are also found to be similar, and there is an indication of certain minor bond-length variations extending over the entire length of the molecule. In the grouping of the molecules in the crystal there is again evidence of a fairly close lateral approach, as well as the usual end-to-end hydrogen bonding through the carboxyl groups. This type of lateral approach appears to be characteristic of the acids of the " even " series. The effect of the hydrogen atoms on the intensities of the *X*-ray reflections is discussed, and it is shown that they make considerable contributions to the structure factors of the large spacing planes. Their presence is also evident on some of the contour maps.

The first three members of the series of normal aliphatic dicarboxylic acids (oxalic, malonic, and succinic) have widely different unit cells and crystal structures. From glutaric acid upwards, however, it has been shown, chiefly by the work of Caspari (*J.*, 1928, 3235; 1929, 2709), that the acids form a well-defined and closely related crystallographic series, composed of two sub-groups, the acids with an even and those with an odd number of carbon atoms in the molecule. The dimensions of the *a* and *b* axes and the angle β are rather similar for both groups, and almost constant for successive members in each group, the chief variant being the *c* axis. The even acids have two centrosymmetric molecules in the unit cell, and the *c* axis gives a measure of the chain length. The odd acids have four molecules in the unit cell, and the length of the *c* axis in this case corresponds to two molecules lying end to end.

In the previous paper (Part V) we have examined the fine structure of adipic acid which may be described as the first normal member of the even series, and have obtained evidence of certain bond-length variations in the saturated chain. To discover whether these effects persist in the higher members of the even series we have now made a similar quantitative *X*-ray investigation of the structure of sebacic acid. Our measurements lead to the rather surprising conclusion that in this saturated chain of ten carbon atoms there are again variations, in the nature of alternate long and slightly shorter bonds, over the entire length of the molecule. It is true that these variations are not much greater than the possible experimental error, but their regularity and their persistence in other members of this series of even acids would seem to be significant.

Another point of interest in this analysis concerns the effect of the hydrogen atoms on the intensities of the *X*-ray reflections. These are usually neglected in *X*-ray work, but if as a first approximation we take the scattering power of an atom to be proportional to its atomic number, then hydrogen is responsible for over 16% of the total scattering matter in sebacic acid. At low angles of reflection this effect should be noticeable, and we find that it has in fact a considerable influence on certain reflections, as well as being apparent in the electron-density maps. We make allowance for this effect in our calculations.

Crystal Data.—Sebacic acid, $C_{10}H_{18}O_4$; *M*, 202·2; m. p. 134°; *d*, calc. 1·226, found 1·231. Monoclinic prismatic, $a = 10{\cdot}10 \pm 0{\cdot}03$, $b = 5{\cdot}00 \pm 0{\cdot}01$, $c = 15{\cdot}10 \pm 0{\cdot}05$ A., $\beta = 133{\cdot}8° \pm 0{\cdot}3°$. Absent spectra, (*h*0*l*) when *h* is odd, (0*k*0) when *k* is odd. Space group $C_{2h}^5(P2_1/a)$. Two molecules per unit cell. Molecular symmetry, centre. Volume of the unit cell, 548 A.^{3}. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$) $\mu = 9{\cdot}08$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 220.

The crystals obtained from most solvents are in the form of very thin flakes developed on the (001) face. These are generally unsuitable for *X*-ray work. Slow and careful crystallisation from amyl acetate, however, sometimes yields crystalline fragments which can be cut to give suitable specimens. Crystals so obtained usually show only the (001) and (100) faces, no end faces being identified with certainty. There is marked cleavage on (001) and (100). Further goniometric and optical data are given by Caspari (*loc. cit.*).

Analysis of the Structure.—Probable positions for the molecules in this crystal have been suggested by Caspari (*loc. cit.*) but the work does not lead to the actual determination of any atomic positions. The asymmetric unit in the structure consists of one half molecule. The dimensions of the *a* and *b* axes are almost identical with those of adipic acid (Part V), and it is clear that the molecular arrangement in the two acids is similar, the additional four carbon atoms in the chain of sebacic acid being accommodated by the increased *c* axis. The similarity

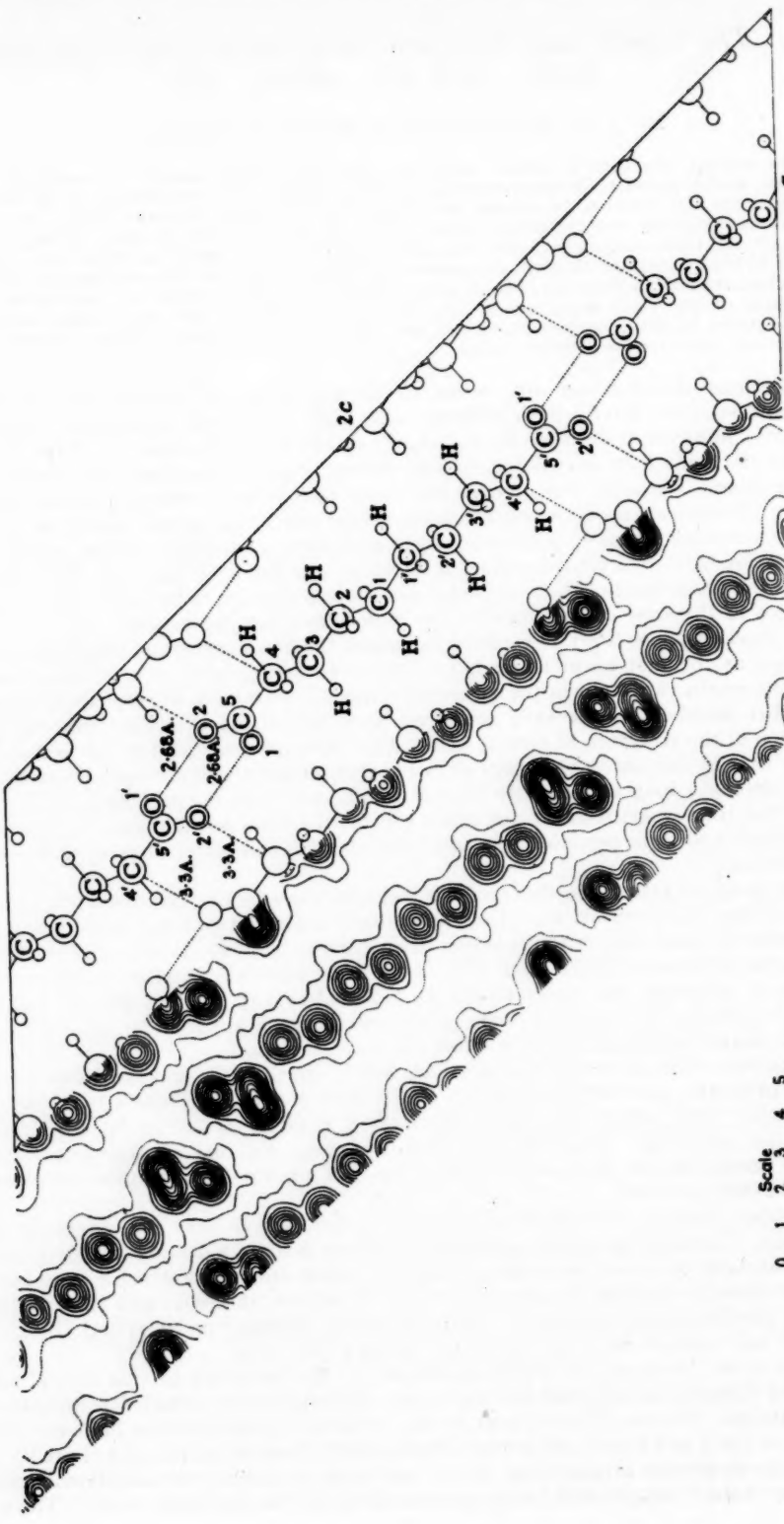


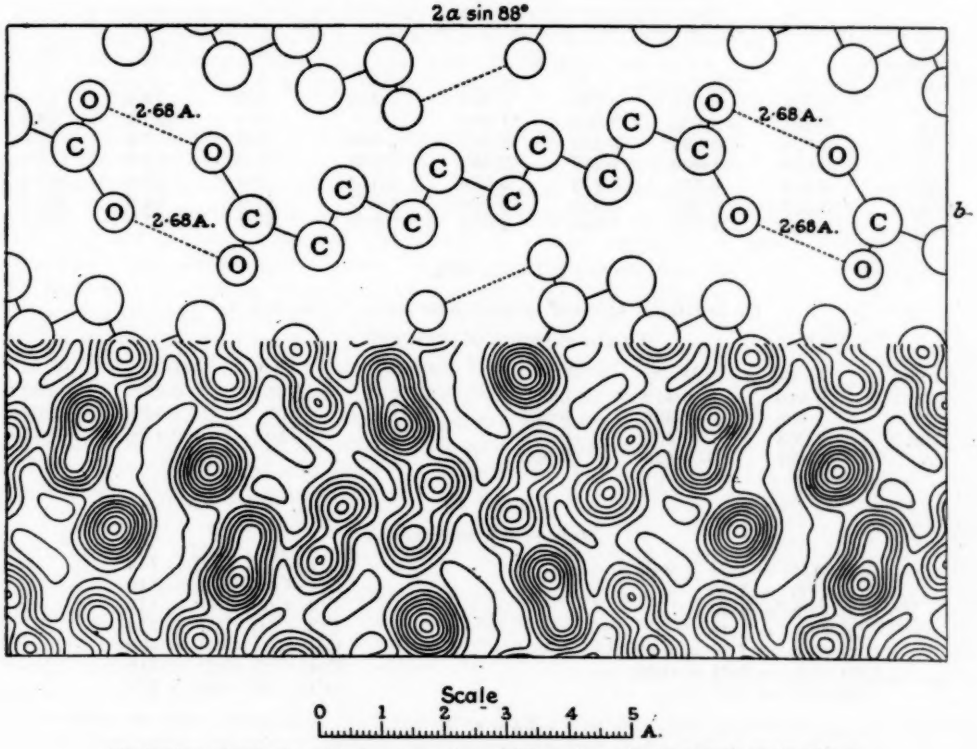
FIG. 1.

Projection of sebacic acid structure along the b *axis on* (010). *Contour scale: one electron per* A.^{2} *per line, one-electron line dotted.*

of the b axes in the two structures also indicates that the inclination of the molecules to the (010) plane must be approximately the same.

From a consideration of these facts, and an examination of the planes of outstanding intensity, notably the (200), (006), (40$\bar{6}$), (40$\bar{1}\bar{2}$), (20$\bar{6}$), and (20$\bar{1}\bar{2}$) planes, it was possible to find by trial a structure which gave fair agreement between the calculated and measured structure factors. In this structure the whole molecule was assumed to be planar. The co-ordinates were then refined by successive double Fourier syntheses, giving projections of the structure on the (010) plane. The final projection is shown in Fig. 1, and from it accurate values of the x and z co-ordinates of all the atoms except C(5) and O(1) can be obtained.

FIG. 2.



Projection of sebacic acid structure along [101] *axis. Contour scale as in Fig.* 1.

The y co-ordinates were first obtained by trial, and then refined by a further Fourier projection made along the [101] axis using the ($hk\bar{h}$) structure factors. This is shown in Fig. 2. All the atoms are resolved in this case except C(5), the position of which is again uncertain. In this projection the atoms are rather crowded and mutual interference tends to reduce the accuracy. Nevertheless, these two projections together give a fairly precise picture of the complete structure.

Orientation, Co-ordinates, and Dimensions.—The mid points of the seven most central carbon–carbon bonds in the molecule are found to lie very accurately on a straight line, which is accordingly chosen as the principal molecular axis, L. The eight central carbon atoms are also very nearly coplanar ($\pm$0·03 A.), and so the second molecular axis M is chosen in this plane, at right angles to L. The third axis N is perpendicular to L and M. The orientation of the molecule in the crystal can then be expressed by giving the angles (χ, ψ, ω) which these molecular axes make with the crystallographic axes a, b, and c', c' being chosen perpendicular to a and b. These angles are given in Table I.

The co-ordinates of the atoms in the asymmetric crystal unit (half the chemical molecule) are given in Table II, as determined from the final Fourier projections. The figures for atom C(5) are perhaps more in doubt than the others, owing to lack of satisfactory resolution, but

the position assigned is fairly well defined by the outer contour levels and cannot be much in doubt. These co-ordinates are referred to the crystallographic axes.

TABLE I.

Orientation of the molecule in the crystal.

$\chi_L = 50{\cdot}3°$, $\cos\chi_L = 0{\cdot}6390$	$\chi_M = 63{\cdot}3°$, $\cos\chi_M = 0{\cdot}4493$	$\chi_N = 51{\cdot}5°$, $\cos\chi_N = 0{\cdot}6230$
$\psi_L = 98{\cdot}2°$, $\cos\psi_L = -0{\cdot}1420$	$\psi_M = 29{\cdot}9°$, $\cos\psi_M = 0{\cdot}8668$	$\psi_N = 118{\cdot}6°$, $\cos\psi_N = -0{\cdot}4780$
$\omega_L = 40{\cdot}9°$, $\cos\omega_L = 0{\cdot}7560$	$\omega_M = 102{\cdot}6°$, $\cos\omega_M = -0{\cdot}2170$	$\omega_N = 128{\cdot}2°$, $\cos\omega_N = -0{\cdot}6189$

TABLE II.

Co-ordinates. Centre of symmetry as origin.

x, y, z are referred to the monoclinic crystal axes, and x', y, z' to the orthogonal axes a, b, and c'.

Atom (cf. Fig. 3).	x, A.	y, A.	z, A.	x', A.	z', A.	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.
C(1)	−0·221	0·270	0·553	0·604	0·399	−7·9°	19·4°	13·2°
C(2)	0·387	−0·630	2·088	1·059	1·507	13·8	−45·4	49·8
C(3)	0·036	−0·094	3·252	2·217	2·346	1·3	− 6·8	77·5
C(4)	0·650	−1·000	4·757	2·646	3·433	23·2	−72·0	113·4
C(5)	0·353	−0·570	5·978	3·789	4·313	12·6	−41·0	142·5
O(1)	−0·501	0·480	5·623	4·396	4·057	−17·9	34·6	134·1
O(2)	1·040	−1·320	7·348	4·050	5·302	37·2	−95·0	175·2

TABLE III.

Co-ordinates referred to molecular axes, L, M, *and* N.

(Origin at centre of symmetry.)

Atom.	L, A.	M, A.	N, A.	Atom.	L, A.	M, A.	N, A.
C(1)	0·649	0·419	0·000	C(5)	5·762	0·272	−0·037
C(2)	1·906	−0·398	0·028	O(1)	5·809	1·510	−0·001
C(3)	3·203	0·406	−0·026	O(2)	6·785	−0·475	−0·128
C(4)	4·427	−0·423	0·002				

TABLE IV.

Molecular dimensions.

C(1′)–C(1) = 1·54 ± 0·02 A.	C(1′)–C(1)–C(2) = 114°
C(1)–C(2) = 1·50 ,,	C(1)–C(2)–C(3) = 115
C(2)–C(3) = 1·53 ,,	C(2)–C(3)–C(4) = 114
C(3)–C(4) = 1·48 ,,	C(3)–C(4)–C(5) = 118
C(4)–C(5) = 1·51 ± 0·03	C(4)–C(5)–O(1) = 120
C(5)–O(1) = 1·24 ± 0·04	C(4)–C(5)–O(2) = 116
C(5)–O(2) = 1·27 ,,	O(1)–C(5)–O(2) = 124

TABLE V.

Intermolecular distances (A.).*

O(1*A*) . . . O(2*C*) = 2·68 ± 0·05	O(2*C*) . . . C(4′*B*) = 3·78 ± 0·05
O(2*A*) . . . O(1*C*) = 2·68 ,,	O(1*A*) . . . C(2*B*) = 3·87 ,,
O(2*C*) . . . C(4*B*) = 3·32 ,,	O(1*A*) . . . C(4*B*) = 3·90 ,,
O(2*A*) . . . O(2*C*) = 3·56 ,,	O(1*A*) . . . C(3*B*) = 3·96 ,,
O(2*C*) . . . O(2*B*) = 3·68 ,,	

* *A* = standard molecule; *B* = reflected molecule; *C* = molecule one translation along *c* axis.

For many purposes it is convenient to list the co-ordinates of the atoms with reference to the molecular axes, *L*, *M*, and *N*, as defined above. These figures are collected in Table III.

The bond lengths and valency angles within the molecule deduced from these co-ordinates are shown in Fig. 3, and collected in Table IV. The central carbon–carbon bond at the centre of symmetry appears to have the normal length of 1·54 A. After that there is a distinct although slight alternation of long and short bonds extending over the entire length of the molecule. The final bonds connecting to the carboxyl groups, C(4)–C(5), are somewhat uncertain but appear to be slightly longer than the bonds C(3)–C(4) immediately adjacent to them. The structure of the carboxyl group is closely similar to that found in the other acids of the series.

The geometry of the molecule is also very similar to that of the other members of the series, except that in sebacic acid the whole molecule appears to be more strictly planar. The eight

central carbon atoms, C(1), C(2), C(3), C(4), C(1′), C(2′), C(3′), and C(4′), probably lie accurately in one plane (±0·03 A.). The plane of the carboxyl group is tilted by approximately 3° from this plane, and the carboxyl-group plane then passes through the centre of symmetry between this molecule and the next molecule along the *c* axis and contains all the atoms of the next adjacent carboxyl group.

Intermolecular Distances.—The general pattern of the intermolecular approach distances, which is indicated by the line drawings in Figs. 1 and 2, is remarkably similar to that found in adipic acid (Part V). In particular, the hydrogen bridges between adjacent carboxyl groups are of the same length (2·68 A.). We also find evidence of an unusually short approach distance (3·32 A.) between the carboxyl oxygen atom O(2) and the carbon atom C(4) of the reflected molecule one translation further along the *c* axis. In adipic acid this distance was 3·29 A. The other approach distances are greater than 3·6 A. The values are collected in Table V.

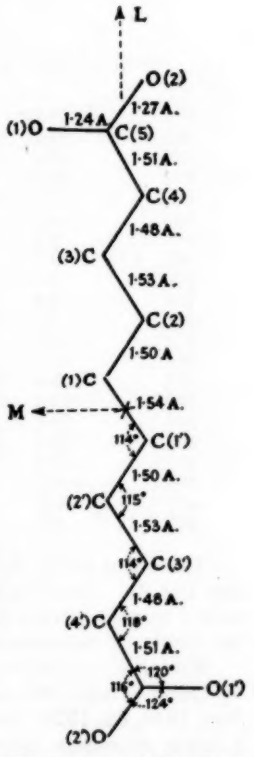
Effect of Hydrogen Atoms on the Intensities of the X-Ray Reflections.—In computing the structure factors for this crystal from the final co-ordinates (see Table VIII), it was noted that the agreement with the measured values for certain large spacing planes remained distinctly poor in spite of careful corrections to the intensities and refinement of the atomic co-ordinates. Further investigation showed that most of these discrepancies could be explained by allowing for the hydrogen atoms, which in sebacic acid account for over 16% of the sum of the atomic numbers.

It is to be expected that hydrogen will make a significant contribution to the total coherent scattering for the low-angle reflections. Atomic scattering curves can be computed, but the allowance for the temperature factor is rather uncertain. In applying the corrections we have accordingly used the following provisional and empirical figures for the hydrogen *f* curve:

sin θ (λ = 1·54) ...	0·0	0·1	0·2	0·3	0·4	0·5	0·6	0·7
f(H)	100	83	58	36	20	8·7	2·9	0

For values of sin θ greater than about 0·4 the corrections are not significant. On the basis of this curve each hydrogen contribution was given a weight of 1 as against a weight of 6 for each carbon and 9 for each oxygen contribution on the empirical carbon–oxygen curve given in the Experimental section.

FIG. 3.



Dimensions of the sebacic acid molecule.

Co-ordinates were assigned to the hydrogen atoms attached to the carbon chain by assuming a carbon–hydrogen distance of 1·09 A. and a tetrahedral distribution of the valency bonds. The resulting co-ordinates are shown in Table VI.

TABLE VI.

Co-ordinates of hydrogen atoms referred to the monoclinic crystal axes and centre of symmetry as origin.

Atom (cf. Fig. 4).	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.	Atom (cf. Fig. 4).	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.
H(1)	−59°	30°	−9°	H(5)	−50°	3°	55°
H(2)	14	88	26	H(6)	22	61	89
H(3)	− 6	−112	38	H(7)	1	−140	101
H(4)	66	− 55	72	H(8)	75	− 82	136

The effect of making corrections for hydrogen on this basis is shown in Table VII, which lists the structure factors for planes with sin θ less than 0·4, and gives the result of the calculation with and without the hydrogen contribution. When the discrepancy is expressed in the usual way as

$$\frac{\Sigma(|F\ \text{meas.}| - |F\ \text{calc.}|)}{\Sigma|F\ \text{meas.}|} \times 100$$

we obtain a figure of 13·8% for the uncorrected F values and only 8·4% for the hydrogen corrected

values. The latter figure is very much better than that usually obtained in *X*-ray investigations of organic structures and seems to indicate that the hydrogen correction is generally significant. It will, of course, be especially important in the case of aliphatic compounds where the proportion of hydrogen in the molecule is relatively high.

TABLE VII.

Structure factors for planes with sin θ <0·4 (λ = 1·54 A.) showing effect of hydrogen.

hkl.	F, meas.	F, calc. with H.	F, calc. without H.	*hkl.*	F, meas.	F, calc. with H.	F, calc. without H.
200	94·0	+103·0	+99·5	$40\bar{3}$	10·0	+ 11·5	+11·5
400	15·0	+ 19·0	+18·0	$40\bar{4}$	25·0	− 24·0	−25·0
001	33·5	− 34·5	−47·5	$40\bar{5}$	32·5	+ 32·0	+33·5
002	11·0	+ 12·5	+17·0	$40\bar{6}$	59·0	− 54·5	−48·0
003	4·0	+ 4·5	+ 4·5	$40\bar{7}$	10·0	+ 8·5	+11·0
004	9·5	− 9·5	− 9·5	011	28·5	− 30·0	−26·5
005	8·0	+ 7·0	+ 7·0	012	3·0	+ 3·5	+ 2·0
020	2·0	+ 1·5	+ 1·5	013	2·5	− 3·0	− 2·0
203	9·0	+ 9·0	+ 8·5	014	6·5	+ 6·5	+ 6·0
202	2·5	− 2·0	− 2·0	015	7·0	+ 3·0	+ 1·5
201	18·5	− 17·5	−17·5	021	27·0	+ 26·5	+26·0
$20\bar{1}$	11·5	+ 11·5	+ 4·0	022	14·5	− 11·5	−11·5
$20\bar{2}$	3·0	− 4·0	0·0	023	11·5	+ 10·5	+11·5
$20\bar{3}$	13·5	+ 14·0	+15·5	$11\bar{1}$	8·5	+ 8·0	+ 5·0
$20\bar{4}$	23·5	− 24·5	−28·5	$12\bar{1}$	11·0	− 8·5	−12·5
$20\bar{5}$	25·5	+ 22·5	+26·0	$21\bar{2}$	15·5	+ 14·5	+15·0
$20\bar{6}$	19·5	− 19·5	−19·0	$22\bar{2}$	7·0	+ 5·0	+ 7·0
$20\bar{7}$	<0·5	+ 0·5	0·0	$31\bar{3}$	<1·0	0·0	+ 0·5
$40\bar{1}$	26·0	+ 28·0	+29·0	$32\bar{3}$	14·0	+ 15·0	+14·0
$40\bar{2}$	9·0	− 8·0	− 8·0	$41\bar{4}$	8·0	− 8·0	− 7·5

The effect of the hydrogen atoms on the electron-density map is fairly clear in Fig. 1 (see also Fig. 4). After this effect was realised, the co-ordinates assigned to the carbon atoms were varied to see whether the positions assigned might be perturbed by the hydrogens, but within the limits of experimental error this was not found to be the case.

The effect of the hydrogen contribution on planes of large spacing has been noticed before, by Bunn (*Trans. Faraday Soc.*, 1939, **35**, 482) and by Hughes and Lipscomb (*J. Amer. Chem. Soc.*, 1946, **68**, 1970), but this would seem to be the first case in which it has been shown to have a really extensive effect.

EXPERIMENTAL.

X-Ray Measurements.—As in the previous investigations in this series, copper *K*-α radiation (λ = 1·54 A.) was used, and the moving-film method was employed to record the intensities.

For the (*h*0*l*) zone the principal crystal specimen, cut from a larger fragment, had cross-section on (010) of 0·30 mm. × 0·11 mm. Relative absorption corrections were not made, as they were found not to be significant for a specimen of this size completely immersed in the *X*-ray beam. To extend the range of intensities, a larger specimen of 1·20 mm. × 0·62 mm. cross-section was used. Combining the results from these specimens, a total of 141 out of a possible 145 reflections were recorded.

For the (*hkh*) zone, a specimen of cross-section 0·55 mm. × 0·45 mm. normal to the rotation axis was used, and for the (0*kl*) zone one of 0·28 mm. × 0·25 mm.

The multiple-film technique (Robertson, *J. Sci. Instr.*, 1943, **20**, 175) was used to correlate the intensities, chiefly by visual estimation, over a total range of about 25,000 to 1. In the different zones, the sets of intensities were correlated by means of their common axial reflections. The usual correction factors were applied, and the structure factors are listed in Table VIII. The absolute scale was obtained by correlation with the values finally calculated from the atomic positions.

Fourier Analysis and Structure Factor Calculations.—The electron-density maps were computed by the usual methods (*idem*, *ibid.*, 1948, **25**, 28). For the projection on (010) the axial subdivisions were $a/60 = 0{\cdot}168$ A., and $c/60 = 0{\cdot}252$ A. For the normal projection along the [101] axis the subdivisions were $b/30 = 0{\cdot}167$ A. and $a \cos 2{\cdot}1°/60 = 0{\cdot}168$ A.

A plot of the asymmetric crystal unit in the (010) projection is shown in Fig. 4, with the centres finally assigned to the atoms shown in relation to the co-ordinate network. In this diagram the positions of the centres assumed for the hydrogen atoms are also shown.

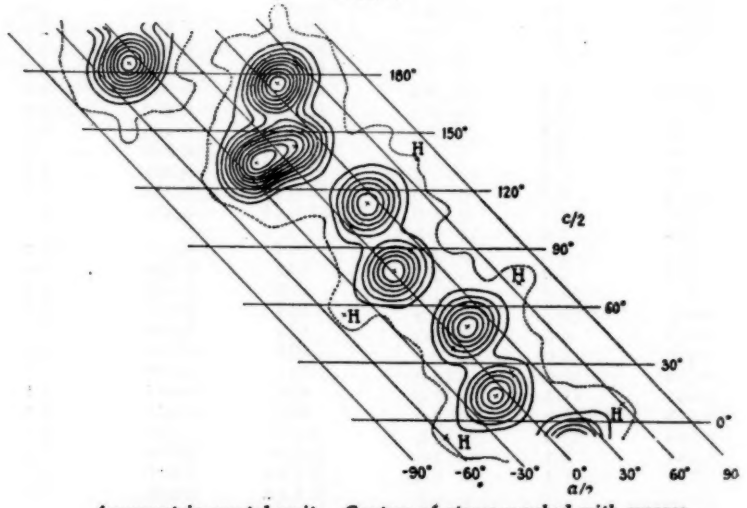
From the final co-ordinates listed in Table II all the structure factors were recalculated and the results are given in Table VIII. The results listed there do not take account of the hydrogen contributions, which are dealt with separately for the large spacing planes in Table VII. For the general calculation of the structure factors the following composite empirical *f*-curve, which appeared to give the best agreement with the observed values, was derived:

$\sin\theta(\lambda = 1{\cdot}54)$	0·0	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9
$f_{(\sigma)}$	100	85	62	44	33	25	18	13	8·8	5·5

On the basis of this composite curve the contributions of the oxygen atoms were weighted relatively to the carbon contributions in the ratio of 1·5 to 1·0.

The discrepancies finally obtained, expressed as percentages in the usual way, were 16·7% for the (*h*0*l*) reflections, 13·2% for the (*hk*$\bar{h}$) reflection, and 15·7% over all. As has been noted above, these agreements can be very greatly improved for the large spacing planes by taking account of the hydrogen contributions.

FIG. 4.



Asymmetric crystal unit. Centres of atoms marked with crosses.

TABLE VIII.

Measured and calculated values of the structure factor.

hkl.	sin θ (λ = 1·54 A.).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54 A.).	F, meas.	F, calc.
200	0·212	94·0	+99·5	20$\bar{1}$	0·171	11·5	+ 4·0
400	0·423	15·5	+18·0	20$\bar{2}$	0·154	3·0	− 0·0
600	0·635	1·0	− 1·5	20$\bar{3}$	0·168	13·5	+15·5
800	0·846	1·5	− 1·0	20$\bar{4}$	0·206	23·5	−28·5
				20$\bar{5}$	0·259	25·5	+26·0
001	0·070	33·5	−47·5	20$\bar{6}$	0·319	19·5	−19·0
002	0·141	11·0	+17·0	20$\bar{7}$	0·383	<0·5	0·0
003	0·212	4·0	+ 4·5	20$\bar{8}$	0·448	9·5	+ 8·0
004	0·282	9·5	− 9·5	20$\bar{9}$	0·514	10·5	− 9·0
005	0·353	8·0	+ 7·0	2,0,$\bar{10}$	0·584	7·0	+ 4·5
006	0·423	18·5	+16·5	2,0,$\bar{11}$	0·653	8·0	− 7·5
007	0·494	15·0	−14·0	2,0,$\bar{12}$	0·720	21·5	−19·5
008	0·564	13·5	+14·0	2,0,$\bar{13}$	0·789	9·5	+ 8·5
009	0·635	8·5	− 8·5	2,0,$\bar{14}$	0·858	4·5	− 4·0
0,0,10	0·705	5·0	+ 5·0	2,0,$\bar{15}$	0·928	1·5	+ 1·0
0,0,11	0·776	10·0	− 9·5				
0,0,12	0·846	5·0	− 5·5	409	0·978	1·5	+ 1·5
0,0,13	0·917	2·0	+ 1·5	408	0·910	1·0	− 0·5
0,0,14	0·987	0·5	0·0	407	0·845	1·0	− 1·0
				406	0·780	2·0	+ 4·0
020	0·308	2·0	+ 1·5	405	0·715	10·0	+11·0
040	0·616	<2·5	− 2·0	404	0·653	4·0	− 4·0
060	0·924	2·0	− 3·0	403	0·589	6·0	+ 8·5
				402	0·530	9·5	−11·0
2,0,11	0·938	4·0	− 4·5	401	0·478	5·0	+ 6·5
2,0,10	0·868	1·0	− 0·0	40$\bar{1}$	0·380	26·0	+29·0
209	0·798	<1·0	− 1·5	40$\bar{2}$	0·344	9·0	− 8·0
208	0·728	4·0	+ 6·0	40$\bar{3}$	0·319	10·0	+11·5
207	0·659	8·0	−10·0	40$\bar{4}$	0·308	25·0	−25·0
206	0·588	10·5	+15·5	40$\bar{5}$	0·314	32·5	+33·5
205	0·521	8·5	+ 8·5	40$\bar{6}$	0·335	59·0	−48·0
204	0·455	7·5	− 6·5	40$\bar{7}$	0·369	10·0	+11·0
203	0·388	9·0	+ 8·5	40$\bar{8}$	0·410	1·0	+ 0·5
202	0·323	2·5	− 2·0	40$\bar{9}$	0·463	7·5	− 7·0
201	0·263	18·5	−17·5	4,0,$\bar{10}$	0·518	7·5	+ 5·5

TABLE VIII.—*continued.*

hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.
4,0,11	0·576	6·0	− 4·5
4,0,12	0·638	36·5	−29·0
4,0,13	0·698	11·0	+10·5
4,0,14	0·761	8·0	− 6·0
4,0,15	0·825	3·0	+ 2·5
4,0,16	0·893	<1·0	0·0
4,0,17	0·960	3·0	− 1·0
606	0·979	0·5	+ 0·5
605	0·918	4·0	+ 5·0
604	0·858	2·5	+ 2·0
603	0·795	2·5	+ 1·0
602	0·740	2·0	− 5·0
601	0·688	3·5	+ 6·0
601	0·590	14·5	+17·0
602	0·549	1·0	+ 1·5
603	0·514	4·0	− 4·0
604	0·488	2·0	− 2·5
605	0·470	11·0	+11·5
606	0·463	29·5	−30·0
607	0·465	6·0	− 6·0
608	0·479	5·0	+ 5·0
609	0·503	10·0	−10·0
6,0,10	0·535	11·5	+11·0
6,0,11	0·573	10·0	− 9·0
6,0,12	0·668	22·5	−19·0
6,0,13	0·686	3·5	− 1·0
6,0,14	0·719	1·5	− 1·0
6,0,15	0·773	1·0	+ 0·5
6,0,16	0·831	2·5	+ 2·0
6,0,17	0·891	4·5	− 1·5
6,0,18	0·953	7·0	+ 4·0
803	0·990	2·5	− 1·5
802	0·950	<0·5	+ 0·5
801	0·900	1·0	+ 1·0
801	0·803	4·5	+ 4·0
802	0·758	2·0	+ 5·5
803	0·720	5·5	− 8·5
804	0·688	6·0	+ 7·0
805	0·660	3·5	− 3·5
806	0·636	3·5	− 6·0
807	0·623	13·5	−16·5
808	0·618	5·0	+ 4·5
809	0·618	5·5	− 6·0
8,0,10	0·628	7·5	+ 9·0
8,0,11	0·645	9·0	− 9·5
8,0,12	0·670	3·0	− 3·5
8,0,13	0·700	11·5	−10·5
8,0,14	0·738	3·5	+ 2·5
8,0,15	0·777	1·0	− 0·0
8,0,16	0·823	1·5	+ 1·5
8,0,17	0·873	4·0	− 2·5
8,0,18	0·922	12·5	+ 7·0
8,0,19	0·978	4·5	− 2·0
10,0,2	0·970	0·5	+ 1·0
10,0,3	0·928	1·0	− 2·5
10,0,4	0·889	2·5	+ 4·0
10,0,5	0·858	2·5	− 4·0
10,0,6	0·828	1·5	+ 0·5
10,0,7	0·806	9·5	−10·5
10,0,8	0·788	3·0	− 2·5
10,0,9	0·776	4·5	+ 3·0
10,0,10	0·770	2·0	+ 0·5
10,0,11	0·771	1·5	− 2·5
10,0,12	0·778	1·0	+ 0·5
10,0,13	0·793	8·0	− 7·5
10,0,14	0·811	1·0	+ 0·5
10,0,15	0·835	2·5	+ 2·5
10,0,16	0·866	3·0	− 4·5
10,0,17	0·902	1·0	+ 1·0
10,0,18	0·940	8·0	+ 4·0
10,0,19	0·983	3·0	+ 0·5
12,0,7	0·990	2·5	− 2·5
12,0,8	0·978	2·5	− 3·5
12,0,9	0·958	4·0	+ 4·0
12,0,10	0·940	3·0	− 2·5
12,0,11	0·930	1·5	+ 1·5
12,0,12	0·925	1·0	− 0·5
12,0,13	0·925	2·0	− 1·5
12,0,14	0·930	1·0	− 1·0
12,0,15	0·941	2·0	+ 2·0
12,0,16	0·958	2·5	− 2·0
12,0,17	0·978	2·5	+ 2·0
011	0·170	28·5	−26·5
012	0·209	3·0	+ 2·0
013	0·262	2·5	− 2·0
014	0·321	6·5	+ 6·0
015	0·384	7·0	+ 1·5
016	0·450	16·5	+21·0
017	0·516	7·5	− 7·5
018	0·585	<2·5	+ 2·0
019	0·654	<2·5	+ 1·5
0,1,10	0·721	3·0	− 2·0
0,1,11	0·788	3·0	− 3·0
0,1,12	0·861	6·5	+ 7·0
0,1,13	0·928	3·0	− 2·5
021	0·315	27·0	+26·0
022	0·339	14·5	−11·5
023	0·373	11·5	+11·5
024	0·417	9·0	− 7·5
025	0·468	28·0	+28·0
026	0·523	10·0	−13·0
027	0·581	<2·5	− 2·0
028	0·642	<2·5	− 0·5
029	0·710	<3·0	+ 2·5
0,2,10	0·770	3·0	− 3·5
0,2,11	0·834	<2·5	+ 1·5
0,2,12	0·900	5·0	− 4·5
0,2,13	0·966	<1·5	− 0·0
031	0·467	3·5	+ 4·0
032	0·483	11·5	−12·5
033	0·507	5·0	+ 5·0
034	0·541	10·0	+11·0
035	0·581	2·5	+ 3·0
036	0·626	3·0	+ 4·0
037	0·676	8·0	+ 8·5
038	0·729	4·5	− 3·5
039	0·785	5·0	+ 5·5
0,3,10	0·843	<2·5	− 4·0
0,3,11	0·903	<2·0	+ 2·5
0,3,12	0·964	<1·5	+ 0·5
041	0·619	<2·5	−1·0
042	0·632	2·5	+ 2·5
043	0·651	6·0	− 7·5
044	0·677	13·5	+18·0
045	0·709	5·5	− 6·0
046	0·747	4·5	+ 3·5
047	0·789	5·0	− 5·5
048	0·835	3·5	− 3·5
049	0·885	3·5	+ 2·0
0,4,10	0·936	<2·0	+ 1·5
051	0·773	<2·5	+ 1·5
052	0·782	<2·5	+ 1·5
053	0·798	3·0	+ 4·0
054	0·820	2·5	+ 2·5

TABLE VIII.—*continued.*

hkl.	sin θ (λ = 1·54).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54).	F, meas.	F, calc.
055	0·846	<2·5	− 2·0	$51\bar{5}$	0·413	10·0	+ 9·0
056	0·878	<2·5	+ 1·5	$52\bar{5}$	0·490	10·5	+11·0
057	0·914	<2·0	− 0·5	$53\bar{5}$	0·600	4·0	+ 6·5
058	0·953	2·0	+ 3·0	$54\bar{5}$	0·725	8·0	+ 9·0
				$55\bar{5}$	0·860	<1·5	− 1·0
061	0·926	2·0	+ 2·5	$56\bar{5}$	0·999	<0·5	− 1·5
062	0·934	2·5	− 3·0				
063	0·947	<1·5	− 0·5	$61\bar{6}$	0·484	9·5	−11·5
064	0·965	<1·5	+ 0·5	$62\bar{6}$	0·553	<1·5	+ 1·5
065	0·989	<1·0	− 0·0	$63\bar{6}$	0·650	2·0	+ 4·5
				$64\bar{6}$	0·768	<1·5	+ 1·5
$11\bar{1}$	0·189	8·5	+ 5·0	$65\bar{6}$	0·895	2·0	− 2·0
$12\bar{1}$	0·326	11·0	−12·5				
$13\bar{1}$	0·474	4·5	+ 4·0	$71\bar{7}$	0·557	9·0	− 8·5
$14\bar{1}$	0·625	2·5	+ 3·5	$72\bar{7}$	0·618	5·5	+ 6·5
$15\bar{1}$	0·776	5·0	+ 5·0	$73\bar{7}$	0·708	2·5	− 4·0
$16\bar{1}$	0·930	<1·0	0·0	$74\bar{7}$	0·815	<1·5	− 1·0
				$75\bar{7}$	0·936	<1·0	− 1·0
$21\bar{2}$	0·218	15·5	+15·0				
$22\bar{2}$	0·344	7·0	+ 7·0	$81\bar{8}$	0·632	6·5	+ 5·5
$23\bar{2}$	0·486	14·5	−14·5	$82\bar{8}$	0·685	12·5	−12·5
$24\bar{2}$	0·635	5·5	− 6·0	$83\bar{8}$	0·767	7·5	+ 9·0
$25\bar{2}$	0·784	4·0	+ 4·5	$84\bar{8}$	0·867	<1·5	+ 1·0
$26\bar{2}$	0·935	2·5	− 2·5	$85\bar{8}$	0·984	<0·5	− 0·5
				$91\bar{9}$	0·705	4·5	+ 3·5
$31\bar{3}$	0·277	<1·0	+ 0·5	$92\bar{9}$	0·755	7·0	− 6·0
$32\bar{3}$	0·384	14·0	+14·0	$93\bar{9}$	0·830	3·0	− 1·5
$33\bar{3}$	0·515	4·0	− 2·5	$94\bar{9}$	0·924	<1·0	− 0·5
$34\bar{3}$	0·657	2·0	+ 2·5	$10,1,\bar{1}0$	0·780	5·0	+ 6·0
$35\bar{3}$	0·807	3·5	− 3·5	$10,2,\bar{1}0$	0·824	<1·5	0·0
$36\bar{3}$	0·950	3·5	+ 3·5	$10,3,\bar{1}0$	0·892	<1·0	+ 1·5
				$10,4,\bar{1}0$	0·982	<0·5	+ 0·5
$41\bar{4}$	0·343	8·0	− 7·5	$11,1,\bar{1}1$	0·855	<1·5	− 1·0
$42\bar{4}$	0·434	9·0	+ 8·0	$11,2,\bar{1}1$	0·896	<1·0	− 2·0
$43\bar{4}$	0·559	6·5	− 7·0	$11,3,\bar{1}1$	0·960	<1·0	− 1·5
$44\bar{4}$	0·687	6·5	+ 5·0				
$45\bar{4}$	0·827	3·5	+ 4·5	$12,1,\bar{1}2$	0·930	<1·0	− 0·5
$46\bar{4}$	0·973	2·0	+ 2·5	$12,2,\bar{1}2$	0·969	<1·0	− 0·5

We thank Imperial Chemical Industries Ltd. for a supply of pure sebacic acid, and for a grant which enabled one of us (J. D. M.) to take part in this work.

UNIVERSITY OF GLASGOW. [*Received, September 27th,* 1948.]

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212. *The Crystal and Molecular Structure of Certain Dicarboxylic Acids. Part VII.* β-*Glutaric Acid.*

By J. D. MORRISON and J. MONTEATH ROBERTSON.

Glutaric acid is the first truly representative member of the well-defined "odd" series of normal aliphatic dicarboxylic acids. A quantitative *X*-ray investigation of the crystal structure is described. The unit cell is doubled as compared with the "even" acids, and there is a space-group change from C_{2h}^5 to C_{2h}^5. The molecule displays a two-fold axis of symmetry instead of a centre. These changes, however, are essentially superficial, and there is a marked general resemblance in the molecular arrangements in the odd and the even series. In fine structure some significant changes are detected. The bond lengths are more closely normal in glutaric acid, and the slight alternating variations detected in the acids of the even series are absent. The carboxyl group also deviates further from the plane of chain carbon atoms. Another significant effect is found in the intermolecular-approach distances. The end-to-end hydrogen bridge connections between the carboxyl groups of adjoining molecules (2·69 A.) are almost the same as in the "even" structures, but the lateral connections (3·6 A. minimum) are much weaker. These facts probably account for some of the outstanding differences in physical properties shown by the acids of the odd and even series.

No precise structure determination has yet been reported for any of the normal aliphatic dicarboxylic acids with an odd number of carbon atoms in the chain, although lattice constants

and space-group data for several members are available (Caspari, *J.*, 1928, 3235; 1929, 2709; Dupré la Tour, *Compt. rend.*, 1932, **194**, 622). It is a matter of considerable interest to determine the general arrangement of the molecules in this series, and also to discover whether the bond-length variations which have been detected in the carbon chains for succinic, adipic, and sebacic acids (Parts IV—VI) also occur in the acids of the odd series.

In the present paper we examine in detail the structure of β-glutaric acid (the crystal modification which is stable at ordinary temperatures). Glutaric acid is the first normal member of the well-defined odd series, as the data available for malonic acid (Gerstäcker, Moller, and Reis, *Z. Krist.*, 1927, **66**, 421) indicate a structure which may differ considerably from that of the higher members of the series.

Although the unit cell in glutaric acid is doubled as compared with the corresponding even acids, and there is a space-group change involving a molecular axis of symmetry instead of a centre, yet the main outlines of the structure which we have now determined are remarkably similar to those of the even acids. This may be seen very readily by comparing the *b* axis projections (Fig. 1) with the corresponding projection of the adipic acid structure (Part V). It would seem, therefore, that the symmetry and space-group changes which are necessarily encountered in passing from the even to the odd series of compounds are not sufficient in themselves to account for the very pronounced differences in physical properties shown by these series, although this has been suggested as an explanation (Muller, *Proc. Roy. Soc.*, 1929, *A*, **126**, 317). One is compelled to seek for a more fundamental cause, probably connected with the fine structure of the molecules themselves. In this connection our present results show a more regular carbon chain in the glutaric acid molecule, and an absence of the alternating bond-length variations which appear to be characteristic of the acids of the even series. There are also some significant differences in the intermolecular-approach distances which are described more fully below. It is likely that these two features of the structure are intimately connected.

Crystal Data.—β-Glutaric acid, $C_5H_8O_4$; *M*, 132·1; m. p. 97·5°; *d*, calc. 1·388, found 1·400. Monoclinic prismatic, $a = 10{\cdot}06 \pm 0{\cdot}03$, $b = 4{\cdot}87 \pm 0{\cdot}01$, $c = 17{\cdot}40 \pm 0{\cdot}05$ A., $\beta = 132{\cdot}6° \pm 0{\cdot}4°$. Absent spectra, (*hkl*) when $h + k + l$ is odd, (*h*0*l*) when either *h* or *l* is odd. Space group, C_s^4 (*Ia*) or C_{2h}^6 (*I*2/*a*) (C_{2h}^6 assumed in this analysis). Four molecules per unit cell. Molecular symmetry, two-fold axis. Volume of the unit cell, 627 A.^{3}. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$ A.), $\mu = 13{\cdot}0$ cm.$^{-1}$. Total number of electrons per unit cell = F(000) = 280.

Glutaric acid is very soluble in most of the common solvents except benzene. The most satisfactory method of obtaining crystal specimens suitable for *X*-ray work proved to be that of making concentrated solutions in ethyl alcohol, and allowing the alcohol to evaporate until the syrup solidified. This method gave large, soft, and sometimes well-formed crystals which were easily cut to suitable dimensions. The crystals generally showed well-developed (001) and (100) faces, with a tendency for elongation in the direction of the *b* axis. There is pronounced cleavage on (111). Further goniometric and optical data are given by Dupré la Tour (*loc. cit.*), who also investigated the crystal structure. Lattice constants and space group were determined, but no analysis of the atomic structure was made.

Analysis of the Structure.—The space group C_s^4 which is available in the hemihedral class of the monoclinic system would only require four asymmetric molecules in the unit cell. In this analysis we assume the space group of higher symmetry, C_{2h}^6, which requires eight asymmetric units to complete the symmetry. The justification for this choice ultimately rests on the success of the analysis as a whole. On this basis (C_{2h}^6) it is necessary to assume a two-fold axis of symmetry, parallel to the *b* crystal axis, passing through the central carbon atom of the molecule. The molecular model, which we assume in accordance with the chemical evidence (Fig. 3) can have this symmetry, and its possible orientation in the crystal is considerably limited (Table I). The analysis of the structure is thereby simplified. The length of the *c* axis (17·4 A.) indicates quite clearly that two molecules must lie end to end within this translation, and they will presumably be connected by hydrogen bridges across the carboxyl groups, as in the other members of the series. In the present case, however, these two molecules will be related by the glide plane *c* instead of by a pure translation as in the case of the even acids.

On the basis of these considerations it proved a matter of no great difficulty to postulate a trial structure which yielded a fair measure of agreement between the observed and the calculated structure factors. The co-ordinates were then refined by carrying out successive double Fourier syntheses giving projections of the structure along the *a* and *b* axes. The final projections are shown in Figs. 1 and 2, and from these maps most of the atomic co-ordinates can be obtained with considerable accuracy.

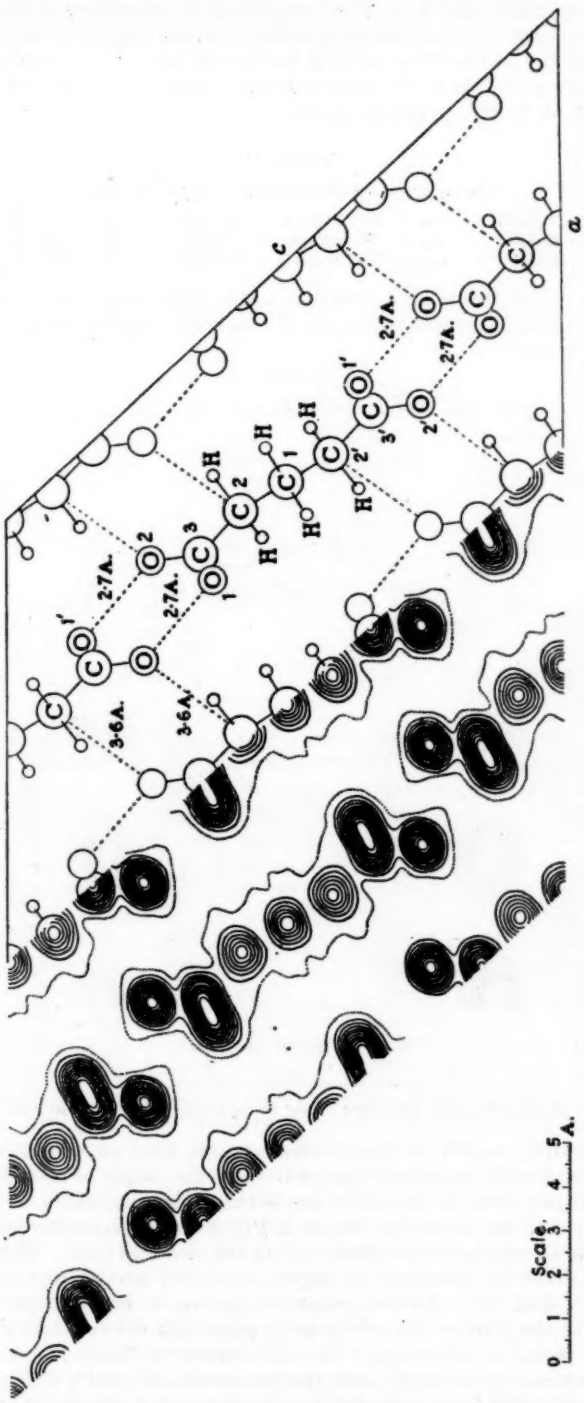


FIG. 1.

Projection of glutaric acid structure along the b *axis on* (010). *Contour scale : one electron per* A.^{2} *per line, one-electron line dotted.*

A synthesis giving a projection of the structure along the [101] axis was also carried out, but the resolution was not satisfactory and it is not reproduced.

Orientation, Co-ordinates, and Dimensions.—The principal molecular axis, *L*, is chosen as the straight line joining the mid-points of the two central carbon–carbon bonds in the molecule

(Fig. 3). The second molecular axis M is the two-fold symmetry axis passing through the central carbon atom, and it is necessarily parallel to the b crystal axis. It must lie at right angles to L, in the plane of the three central carbon atoms. N is perpendicular to L and M. The orientation of the molecule in the crystal is then given by the angles in Table I, the same notation being used as in the previous papers.

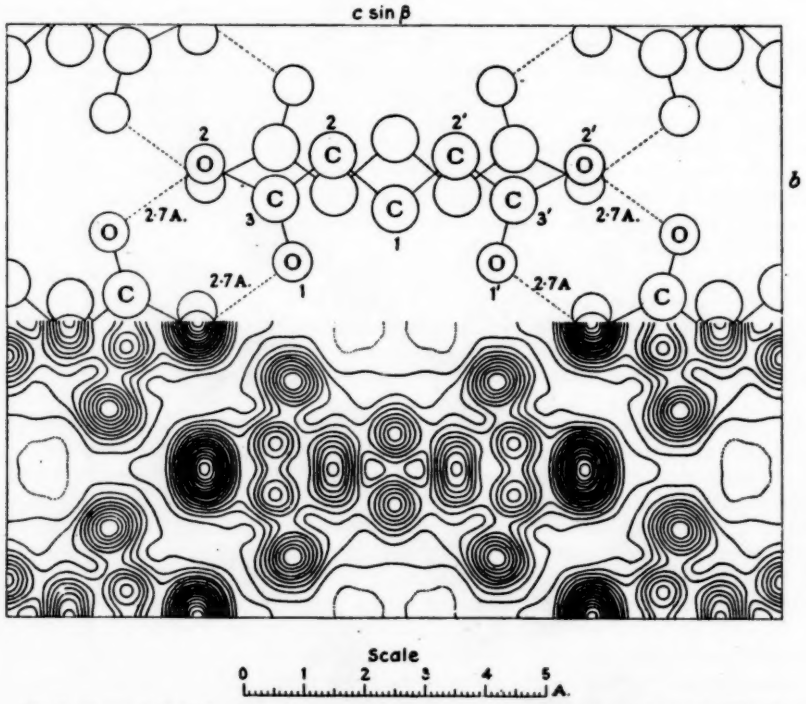
TABLE I.

Orientation of the molecule in the crystal.

$\chi_L = 57{\cdot}7°$, $\cos\chi_L = 0{\cdot}5343$	$\chi_M = 90°$, $\cos\chi_M = 0{\cdot}0000$	$\chi_N = 32{\cdot}3°$, $\cos\chi_N = 0{\cdot}8455$
$\psi_L = 90{\cdot}0°$, $\cos\psi_L = 0{\cdot}0000$	$\psi_M = 0°$, $\cos\psi_M = 1{\cdot}0000$	$\psi_N = 90{\cdot}0°$, $\cos\psi_N = 0{\cdot}0000$
$\omega_L = 32{\cdot}3°$, $\cos\omega_L = 0{\cdot}8455$	$\omega_M = 90°$, $\cos\omega_M = 0{\cdot}0000$	$\omega_N = 122{\cdot}3°$, $\cos\omega_N = -0{\cdot}5343$

The co-ordinates of the atoms with reference to the molecular axes, L, M, and N, as defined above, are given in Table III, from which the dimensions may be compared with those of the other acids in this series.

FIG. 2.



Projection of glutaric acid structure along the a *axis. Contour scale as in Fig.* 1.

The co-ordinates with respect to the crystallographic axes are given in Table II. In this space group (C_{2h}^6) it is usually most convenient to refer the origin of co-ordinates to a centre of symmetry. The centre chosen in this case lies between the molecules, at $a/4$ from the centre of a molecule (Fig. 1). In the projection shown in Fig. 1 there is an apparent centre of symmetry at the centre of the molecule, which is viewed along the two-fold axis. This is not a true centre of symmetry but it gives the structure an appearance very similar to that of adipic acid and sebacic acid (Parts V and VI). In the projection shown in Fig. 2 there is also an apparent centre of symmetry at the intersection of the glide plane and the two-fold axis, but again this is only a centre when viewed in projection. The co-ordinates in Table II are therefore referred to the true centre of symmetry as origin, and the figures consequently differ rather widely from those of the even acids, which are referred to true centres of symmetry at the centres of the molecules.

In Table III, however, the co-ordinates are referred to the intersection of the molecular axes as origin, and this point lies at $(-0{\cdot}250a, 0{\cdot}031b, 0)$ with respect to the crystallographic origin. These co-ordinates are comparable with the corresponding figures given for the other acids.

The bond lengths and valency angles deduced for the glutaric acid molecule are shown in Fig. 3, and the figures are collected in Table IV.

TABLE II.

Co-ordinates. Centre of symmetry as origin.

x, y, z, refer to the monoclinic crystal axes, and x', y, z', to the orthogonal axes a, b, and their perpendicular c'.

Atom (cf. Fig. 3).	x, A.	y, A.	z, A.	x', A.	z', A.	$\frac{2\pi x}{a}$.	$\frac{2\pi y}{b}$.	$\frac{2\pi z}{c}$.
C(1)	−2·515	0·593	0·000	2·515	0·000	− 90·0°	43·8°	0·0°
C(2)	−2·216	−0·288	1·138	3·181	1·053	− 79·3	−21·2	29·7
C(3)	−2·347	0·419	2·682	4·162	1·980	− 84·0	31·0	55·5
O(1)	−3·172	1·474	2·296	4·722	1·694	−113·5	109·0	47·5
O(2)	−1·447	−0·149	4·253	4·325	3·139	− 51·8	−11·0	88·0

TABLE III.

Co-ordinates referred to molecular axes L, M, *and* N.

Atom.	L, A.	M, A.	N, A.	Atom.	L, A.	M, A.	N, A.
C(1)	0·000	0·441	0·000	O(1)	2·612	1·322	0·961
C(2)	1·246	−0·441	0·000	O(2)	3·622	−0·302	−0·146
C(3)	2·554	0·267	0·335				

TABLE IV.

Molecular dimensions.

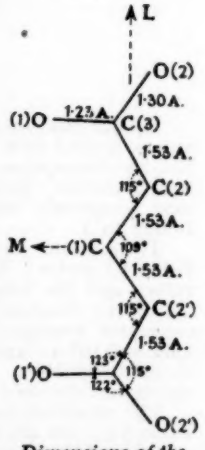
C(1)–C(2) = 1·53 ± 0·02 A.	C(2′)–C(1)–C(2) = 109°
C(2)–C(3) = 1·53 ± 0·03	C(1)–C(2)–C(3) = 115
C(3)–O(1) = 1·23 ,,	C(2)–C(3)–O(1) = 123
C(3)–O(2) = 1·30 ,,	C(2)–C(3)–O(2) = 115
	O(1)–C(3)–O(2) = 122

Within the experimental limits the carbon–carbon bonds lengths appear to be normal, and there is no evidence for alternating long and short bonds of the type that have been reported for all the acids of the "even" series. This observation is of considerable theoretical interest but too much weight should probably not be attached to it until it can be confirmed either by a more detailed (three-dimensional) investigation of this acid, or by similar observations on, further members of the "odd" series.

There are, however, two other ways in which the glutaric acid structure differs considerably from that of the members of the "even" series. The first concerns the geometry of the molecule in the crystal, and the second the intermolecular-approach distances.

With regard to the geometry of the molecule it is found that the planes of the carboxyl groups are inclined at about 32° to the plane of the three central carbon atoms of the chain. This compares with a corresponding deviation in sebacic acid of only about 3°, and in adipic acid of about 6°. Most of the 32° inclination in glutaric acid is due to rotation of the carboxyl group about the C(2)–C(3) bond, but the atom C(3) is also raised above the plane of the three central atoms by 0·33 A., indicating a rotation about the C(1)–C(2) bond of about 14°.

FIG. 3.



Dimensions of the glutaric acid molecule.

Intermolecular Distances.—The more important approach distances between the molecules are indicated by dotted lines on the right hand part of Fig. 1, and the distances which are less than 4 A. are collected in Table V. The closest approaches are again found in the pair of strong hydrogen bridges which connect adjoining carboxyl groups. The distance here, 2·69 A., is closely similar to that found in all the other aliphatic acids examined.

The lateral connections of the glutaric acid molecules, however, are strikingly different in one respect. There is no other distance less than 3·59 A. The unusual bond of about 3·3 A., which exists in adipic and sebacic acid between one of the carboxyl oxygen atoms and the second carbon atom in the chain of an adjoining molecule, has disappeared and is replaced by an approach of 3·59 A., which can only have significance as a relatively weak van der Waals attraction.

TABLE V.

Intermolecular distances (A.).*

O(1A) . . . O(2C)	= 2·69 ± 0·05	O(1A) . . . C(2B)	= 3·74 ± 0·05
O(2A) . . . O(1C)	= 2·69 ,,	O(2C) . . . C(2B′)	= 3·77 ,,
O(2C) . . . C(2B)	= 3·59 ,,	O(2C) . . . O(2B)	= 3·71 ,,
O(1A) . . . C(2′B)	= 3·69 ,,	O(1A) . . . C(1B)	= 3·89 ,,

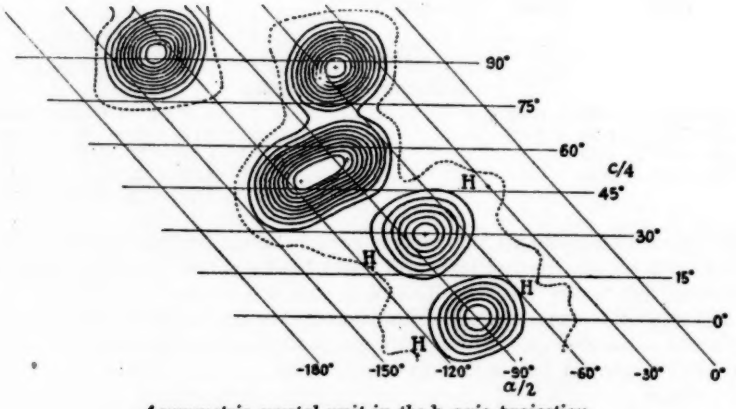
* *A* = standard molecule; *B* = reflected molecule; *C* = molecule one translation along *c* axis.

This difference in structure is no doubt responsible for some of the outstanding physical properties of the glutaric acid crystals, such as their relatively low melting point and soft texture. It is probably one of the fundamental points of difference between the acids of the odd and even series.

EXPERIMENTAL.

X-Ray Measurements.—Copper *K*-α radiation (λ = 1·54 A.) was used throughout the investigation. Rotation and oscillation photographs were taken for the preliminary measurements, but all the intensity records were made on a special type of moving-film camera adapted for easy manipulation of the film packs required for the multiple-film technique, and with screens capable of fine adjustment to cut down the background to a minimum (Robertson, *J. Sci. Instr.*, in the press).

FIG. 4.



Asymmetric crystal unit in the b *axis projection.*

For the (*h*0*l*) zone the principal crystal specimen was cut to a cross-section of 0·14 mm. × 0·25 mm. normal to the *b* axis. For the weaker reflections a larger specimen (0·28 mm. × 0·50 mm.) was employed. Relative absorption corrections were not applied. In all, a total of 80 out of a possible 86 reflections were recorded. For the (0*kl*) and (*hk*$\bar{h}$) zones specimens of similar size were used. All the crystals were completely immersed in the *X*-ray beam. The total range of intensities recorded was about 10,000 to 1.

The structure factors were calculated by the usual theory for mosaic-type crystals, and are given in Table VI under " F, meas." The absolute scale was obtained by correlation between the measured values and the values finally calculated from the co-ordinates.

Fourier Analysis and Calculations.—The structure was first determined by trial and then refined by successive Fourier syntheses. For the projections along the *b* axis the axial subdivisions were $a/60 = 0{\cdot}167$ A. and $c/60 = 0{\cdot}290$ A., and for those along the *a* axis, $b/30 = 0{\cdot}167$ A. and $a \sin\beta/60 = 0{\cdot}214$ A. The usual three-figure methods were employed. The positions finally assigned to the atoms, imposed on the co-ordinate network, are marked in Fig. 4.

The structure factors were recalculated from the final co-ordinates and the results are shown in Table VI. No allowance was made for the hydrogen atoms in this structure although there is some evidence of their effects in the electron-density maps, and in the discrepancies found in the calculations for some of the large spacing planes. A single composite atomic scattering curve was used, with the following *f* values:

$\sin\theta(\lambda = 1{\cdot}54)$	0·0	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9
$f_{(c)}$	100	81	62	45	33	25	19	15	10	6·3

The figures differ slightly from those used for adipic and sebacic acids. It is to be expected that a slightly different average temperature factor will apply. On the basis of this curve the oxygen contributions were weighted relative to the carbon contributions in the ratio of 1·5 to 1·0. The average discrepancies finally obtained in the structure factor calculations, expressed in the usual way, were 18·5% for the (*h*0*l*) planes, 14·5% for the (0*kl*) planes, and 18·6% overall.

TABLE VI.

Measured and calculated values of the structure factor.

hkl.	sin θ (λ = 1·54 A.)	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54 A.).	F, meas.	F, calc.
200	0·208	96·5	−115·5	80$\bar{8}$	0·615	6·5	+ 4·0
400	0·416	9·5	+ 10·0	8,0,$\bar{10}$	0·612	14·0	− 14·5
600	0·624	2·0	+ 4·5	8,0,$\bar{12}$	0·633	22·0	+ 23·0
800	0·832	5·0	+ 2·5	8,0,$\bar{14}$	0·672	2·0	− 1·0
				8,0,$\bar{16}$	0·729	13·0	+ 10·5
002	0·119	28·0	− 37·5	8,0,$\bar{18}$	0·804	2·5	− 1·5
004	0·238	20·0	− 19·5	8,0,$\bar{20}$	0·888	15·0	+ 9·5
006	0·357	15·5	− 13·5	8,0,$\bar{22}$	0·981	13·0	− 5·0
008	0·476	41·5	+ 39·0				
0,0,10	0·595	22·0	− 20·5	10,0,$\bar{2}$	0·959	3·0	− 4·0
0,0,12	0·714	18·0	+ 15·5	10,0,$\bar{4}$	0·891	1·5	− 8·0
0,0,14	0·833	7·5	+ 5·5	10,0,$\bar{6}$	0·835	5·5	+ 9·0
0,0,16	0·952	3·5	+ 4·0	10,0,$\bar{8}$	0·793	7·0	− 9·5
				10,0,$\bar{10}$	0·769	5·5	+ 4·0
020	0·312	30·5	+ 32·5	10,0,$\bar{12}$	0·763	3·0	− 3·5
040	0·624	3·0	+ 3·5	10,0,$\bar{14}$	0·775	2·0	+ 2·0
060	0·936	3·5	− 0·5	10,0,$\bar{16}$	0·805	12·5	− 12·5
				10,0,$\bar{18}$	0·854	1·5	− 3·5
2,0,14	0·995	<0·5	− 0·0	10,0,$\bar{20}$	0·915	5·0	− 2·5
2,0,12	0·875	9·0	− 6·5	10,0,$\bar{22}$	0·988	<1·0	+ 3·0
2,0,10	0·758	3·5	− 1·0				
208	0·640	20·0	− 19·5	12,0,$\bar{8}$	0·982	1·0	+ 2·0
206	0·524	11·0	+ 11·0	12,0,$\bar{10}$	0·945	<1·0	+ 2·5
204	0·413	24·0	+ 24·0	12,0,$\bar{12}$	0·922	6·0	− 7·5
202	0·304	15·0	− 15·5	12,0,$\bar{14}$	0·914	6·0	+ 5·0
20$\bar{2}$	0·155	6·5	+ 9·5	12,0,$\bar{16}$	0·922	5·0	+ 5·0
20$\bar{4}$	0·185	30·0	+ 38·0	12,0,$\bar{18}$	0·946	3·5	+ 4·5
20$\bar{6}$	0·270	42·0	− 42·0	12,0,$\bar{20}$	0·985	<1·0	+ 5·0
20$\bar{8}$	0·374	10·0	− 9·0				
2,0 $\bar{10}$	0·486	23·5	+ 22·5	011	0·168	50·0	+47·5
2,0,$\bar{12}$	0·599	15·0	− 11·5	013	0·239	5·0	− 6·0
2,0,$\bar{14}$	0·717	29·0	− 28·5	015	0·336	3·5	+ 3·0
2,0,$\bar{16}$	0·833	7·5	+ 4·0	017	0·445	10·5	− 6·5
2,0,$\bar{18}$	0·957	3·5	+ 2·5	019	0·558	4·5	− 1·0
				0,1,11	0·671	5·0	+ 6·0
4,0,10	0·935	4·5	+ 8·0	0,1,13	0·789	15·0	+15·0
408	0·822	4·5	− 2·5	0,1,15	0·904	4·5	− 3·0
406	0·711	6·0	+ 3·0				
404	0·603	19·5	− 21·0	022	0·335	30·5	−22·0
402	0·504	24·0	+ 29·0	024	0·394	34·5	+33·0
40$\bar{2}$	0·346	25·0	+ 30·0	026	0·475	27·0	−25·0
40$\bar{4}$	0·309	29·0	− 29·0	028	0·569	<3·5	− 1·0
40$\bar{6}$	0·317	71·5	+ 70·5	0,2,10	0·672	7·5	− 7·5
40$\bar{8}$	0·368	45·5	− 38·0	0,2,12	0·779	17·5	+18·5
4,0,$\bar{10}$	0·444	10·0	− 8·5	0,2,14	0·890	3·0	− 4·5
4,0,$\bar{12}$	0·537	14·5	+ 8·0				
4,0,$\bar{14}$	0·639	49·0	+ 44·5	031	0·473	11·0	+ 9·5
4,0,$\bar{16}$	0·744	21·5	− 16·5	033	0·502	17·5	−17·0
4,0,$\bar{18}$	0·861	1·5	+ 0·5	035	0·555	13·0	−11·5
4,0,$\bar{20}$	0·974	1·5	+ 0·5	037	0·626	<4·0	+ 1·5
				039	0·711	<4·0	+ 3·5
606	0·909	4·0	− 3·0	0,3,11	0·804	6·0	− 9·0
604	0·807	2·5	+ 3·5	0,3,13	0·903	<3·0	− 1·5
602	0·712	5·0	− 8·0				
60$\bar{2}$	0·548	21·0	− 21·5	042	0·636	7·5	−13·0
60$\bar{4}$	0·493	<1·5	− 8·5	044	0·668	<4·0	+ 4·5
60$\bar{6}$	0·462	24·5	− 24·5	046	0·718	13·5	−12·5
60$\bar{8}$	0·463	28·0	+ 25·5	048	0·785	<3·5	+ 5·0
6,0,$\bar{10}$	0·493	12·0	+ 7·5	0,4,10	0·863	<3·0	− 4·5
6,0,$\bar{12}$	0·551	25·0	− 20·5	0,4,12	0·948	<2·5	− 1·0
6,0,$\bar{14}$	0·623	26·5	− 28·0				
6,0,$\bar{16}$	0·707	11·5	+ 8·5	051	0·781	11·5	−13·5
6,0,$\bar{18}$	0·808	<2·0	0·0	053	0·799	8·0	+ 8·5
6,0,$\bar{20}$	0·910	10·5	− 6·0	055	0·834	<3·5	+ 4·0
				057	0·883	7·5	− 8·0
802	0·918	4·5	− 6·5	059	0·945	<2·5	− 0·0
80$\bar{2}$	0·755	7·5	+ 9·0				
80$\bar{4}$	0·690	11·0	+ 22·0	062	0·943	<2·5	− 1·5
80$\bar{6}$	0·643	8·0	− 10·5	064	0·965	<2·0	+ 2·0

TABLE VI—*continued.*

hkl.	sin θ (λ = 1·54 A.).	F, meas.	F, calc.	*hkl.*	sin θ (λ = 1·54 A.).	F, meas.	F, calc.
12$\bar{1}$	0·323	12·0	− 5·0	24$\bar{2}$	0·641	5·5	+ 6·5
22$\bar{3}$	0·348	22·0	−24·5	34$\bar{3}$	0·664	10·0	+12·5
32$\bar{3}$	0·389	19·5	−12·0	44$\bar{4}$	0·695	2·5	− 7·0
42$\bar{4}$	0·439	27·5	−27·5	54$\bar{5}$	0·733	9·0	+11·0
52$\bar{5}$	0·496	8·0	− 7·5	64$\bar{6}$	0·776	5·0	+ 1·0
62$\bar{6}$	0·560	2·5	− 1·0	74$\bar{7}$	0·824	2·0	+ 3·0
72$\bar{7}$	0·623	16·5	−18·0	84$\bar{8}$	0·876	2·5	− 2·0
82$\bar{8}$	0·691	9·5	+14·5	94$\bar{9}$	0·931	4·5	+ 3·5
92$\bar{9}$	0·759	8·0	+ 7·5	10,4,$\bar{10}$	0·990	<1·0	+ 1·0
10,2,$\bar{10}$	0·831	10·0	+15·0				
11,2,$\bar{11}$	0·902	<1·5	− 1·0	16$\bar{1}$	0·940	9·0	− 6·5
12,2,$\bar{12}$	0·974	<1·0	− 2·5	26$\bar{2}$	0·950	2·0	+ 2·5
				36$\bar{3}$	0·966	<1·0	− 2·5
14$\bar{1}$	0·628	5·0	− 5·0	46$\bar{4}$	0·987	<1·0	+ 0·5

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213. *Nitration Products of 5-Aminoacridine, and the Synthesis of 1 : 5- and 4 : 5-Diaminoacridine.*

By A. HAMPTON and D. MAGRATH.

The nitration of 5-aminoacridine gave 3 : 7-*dinitro-5-aminoacridine*, 1 : 3 : 7-*trinitro-5-aminoacridine*, and 1 : 3 : 7-*trinitroacridone*. The last compound, which arises by hydrolysis of the trinitro-amine was identified by synthesis from 2 : 4 : 4′-*trinitrodiphenylamine-2′-carboxylic acid*. It was also isolated after the nitration of 3-nitroacridone. 3 : 5 : 7-*Triaminoacridine* and 1 : 5- and 4 : 5-*diaminoacridine* were also prepared.

AN unorientated dinitro-derivative was obtained from 5-aminoacridine by Meister, Lucius, and Brüning (G.P. 364,033). It has now been found that nitration of 5-aminoacridine below 5° in concentrated sulphuric acid with nitric acid (2·1 mols.) affords 3 : 7-*dinitro-* and 1 : 3 : 7-*trinitro-5-aminoacridine*. These compounds are hydrolysed to the corresponding nitroacridones, the ease of hydrolysis being expressed by the sequence 5-amino- (cf. Albert and Ritchie, *J.*, 1943, 458) < 3 : 7-dinitro-5-amino- < 1 : 3 : 7-trinitro-5-amino-acridine. The structure of the dinitro-compound was established by preparing it from 3 : 7-dinitroacridone (Lehmstedt, *Ber.*, 1931, **64**, 2381) by successive treatment with phosphoryl chloride in nitrobenzene solution (cf. Walls, *J.*, 1945, 294) and with ammonium carbonate in presence of phenol (cf. Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169T). Since the dinitroaminoacridine had no m. p., the identity of the specimens prepared by the alternative methods was established by reducing them to 3 : 5 : 7-*triaminoacridine*. Similarly, the acridone obtained by hydrolysis of the dinitro-5-aminoacridine was reduced to 3 : 7-diaminoacridone, identical with a specimen prepared by reducing 3 : 7-dinitroacridone.

The constitution of the trinitro-5-aminoacridine was determined by an independent synthesis of the 1 : 3 : 7-*trinitroacridone* which it gave on hydrolysis. This acridone was obtained by the action of phosphoryl chloride on 2 : 4 : 4′-*trinitrodiphenylamine-2′-carboxylic acid*, prepared either by nitrating 2 : 4-dinitrodiphenylamine-2′-carboxylic acid (Schroeter and Eisleb, *Annalen*, 1909, **367**, 101), or, in poor yield, by synthesis from 1-chloro-2 : 4-dinitrobenzene and 5-nitro-anthranilic acid. 1 : 3 : 7-Trinitroacridone was also obtained as a by-product in the nitration of 3-nitroacridone.

The yield of 5-chloro-1-nitroacridine was considerably improved by using nitrobenzene at 180° in place of xylene as solvent in the reaction of 1-nitroacridone with phosphoryl chloride (Albert and Gledhill, *loc. cit.*). There was considerable decomposition when ammonia was passed into a solution of 5-chloro-1-nitroacridine at 110°, but 1-nitro-5-aminoacridine was obtained in 76% yield at 60°, a lower temperature than hitherto employed in the amination of 5-chloroacridines. The nitro-amine was converted into 1 : 5-*diaminoacridine* by reduction with stannous chloride. The mixture of 5-chloro-2- and -4-nitroacridines prepared from 3-nitrodiphenylamine-2′-carboxylic acid and phosphoryl chloride (Lehmstedt and Schrader, *Ber.*, 1937, **70**, 838) was aminated by the same method, and 4-nitro-5-aminoacridine, extracted from the resulting mixture of nitro-amines with chloroform, was reduced to 4 : 5-*diaminoacridine* with nascent ferrous carbonate (Albert and Gledhill, *J. Soc. Chem. Ind.*, 1942, **61**, 159T). Some physical and antibacterial

properties of 1 : 5- and 4 : 5-diaminoacridine are reported by Albert and Goldacre (*Nature*, **1948**, **161**, 95); their preparation completes the series of diaminoacridines having an amino-group in position 5 (Albert and Gledhill, *loc. cit.*, 1942; Albert and Ritchie, *loc. cit.*).

Experimental.

The chloronitroacridines described here have a very labile chlorine atom and are strongly irritant to delicate portions of the skin.

Nitration of 5-Aminoacridine.—5-Aminoacridine (5 g.) was dissolved in concentrated sulphuric acid (20 ml.), and concentrated nitric acid (3·54 ml., *d* 1·41, 5% excess) dropped in during 1 hour, the temperature being kept between 0° and 5°. After standing overnight, the mixture was poured into a stirred mixture of ice (250 g.) and water (500 ml.). The orange product was immediately filtered off and, after being washed with cold water, suspended in hot water (150 ml.). This mixture was made slightly alkaline with ammonia, boiled for 5 minutes, cooled, and filtered. The solid, after removal of a little red impurity (probably 3-nitro-5-aminoacridine) by boiling with alcohol (50 ml.), weighed 4·50 g. and on recrystallisation from pyridine gave red needles which at 120° lost solvent and became orange; yield, 3·40 g. (47%) (Found: N, 19·9. Calc. for dinitroaminoacridine, $C_{13}H_8O_4N_4$: N, 19·7%).

The dilute sulphuric acid filtrate was boiled for 10 minutes, and the yellow precipitate (2·03 g., m. p. 260—270°) collected. After one recrystallisation from glacial acetic acid (200 ml., concentrated to *ca.* 100 ml.) and five from acetone (250 ml./g., concentrated to crystallisation), use being made of a mixture of kieselguhr and charcoal to remove an orange-coloured impurity, the 1 : 3 : 7-*trinitroacridone* was obtained as bright yellow needles, m. p. 277° (Found: C, 47·2; H, 1·9; N, 16·8. $C_{13}H_6O_7N_4$ requires C, 47·3; H, 1·8; N, 17·0%).

If the filtrate was run into a slight excess of 8N-ammonia solution (120 ml.), and the red gelatinous precipitate flocculated by warming, an orange solid (2·2 g.) was obtained. This was dissolved in boiling alcohol (225 ml.), the solution filtered, and the filtrate concentrated to half volume. The crystalline product, after two recrystallisations from alcohol, formed red needles (0·93 g.), m. p. 284° (decomp.), of 1 : 3 : 7-*trinitro-5-aminoacridine* (Found: C, 47·5; H, 2·2; N, 21·0. $C_{13}H_7O_6N_5$ requires C, 47·4; H, 2·1; N, 21·3%). The compound dissolved easily in cold dilute sulphuric acid and the solution when heated or kept deposited the insoluble 1 : 3 : 7-trinitroacridone. The trinitroaminoacridine was almost insoluble in water and benzene, moderately soluble in alcohol, easily soluble in acetone and pyridine. Solutions in dilute hydrochloric acid fluoresced a yellow-green.

5-*Chloro*-3 : 7-*dinitroacridine.*—A mixture of 3 : 7-dinitroacridone (Lehmstedt, *loc. cit.*, 1931) (5 g.), phosphorus oxychloride (25 g.), nitrobenzene (38 ml.), and one drop of concentrated hydrochloric acid was heated under reflux in an oil-bath at 180° for 8 hours, complete dissolution occurring in 1 hour. After vacuum evaporation the residue was ground and added with stirring to a mixture of ice and excess of ammonia. The solid was collected and dried in a vacuum (5·96 g.). This was used without further purification for the preparation of 3 : 7-dinitro-5-aminoacridine.

Heating of 3 : 7-dinitroacridone with phosphorus pentachloride in chlorobenzene or nitrobenzene solution did not give appreciable amounts of the 5-chloro-compound, and heating with phosphorus oxychloride alone gave low yields.

3 : 7-*Dinitro-5-aminoacridine.*—An intimate mixture of 5-chloro-3 : 7-dinitroacridine (2·38 g.) and ammonium carbonate (1 g.) was added in portions to phenol (10 g.) at 110°, and the mixture kept at 120° for 1 hour; the phenol was removed by steam distillation, the residual solution made ammoniacal, and the mixture boiled for 5 minutes, cooled, and filtered. The solid was boiled with dilute sulphuric acid (5% v./v., 1600 ml.) for a few minutes, and the filtrate cooled immediately to prevent hydrolysis. The orange needles of the sulphate were filtered off and suspended in hot water (100 ml.), and a slight excess of ammonia added. The orange *base* weighed 1·02 g. (51%, from the acridone). For analysis it was recrystallised from pyridine (25 ml.) (Found: C, 55·0; H, 2·86; N, 19·8. $C_{13}H_8O_4N_4$ requires C, 54·9; H, 2·84; N, 19·7%). Prolonged boiling of the amine with dilute acids, mineral or organic, resulted in hydrolysis to the acridone, the rate of hydrolysis being greater in the case of the organic acids used, *i.e.*, oxalic, acetic, and citric.

3 : 7-Dinitro-5-aminoacridine was insoluble in water and benzene, very slightly soluble in alcohol, slightly in hot acetone, easily in hot pyridine. Solutions in dilute hydrochloric acid and alcohol showed a greenish-yellow fluorescence.

3 : 5 : 7-*Triaminoacridine.*—3 : 7-Dinitro-5-aminoacridine (5 g.) was added cautiously to a boiling solution of stannous chloride dihydrate (31 g.) in concentrated hydrochloric acid (40 ml.). The mixture was heated on a steam-bath for 30 minutes and then cooled, and the yellow double salt filtered off and washed with cold concentrated hydrochloric acid. After dissolution in cold water (300 ml.), the base was obtained as an old-gold, crystalline precipitate by addition of excess of aqueous 30% sodium hydroxide. It was dissolved in 5% acetic acid (70 ml.), the solution clarified, and the base reprecipitated. The yield after vacuum drying was 3·87 g. (98%); m. p. 245° (decomp.). It crystallised from alcohol–light petroleum as yellow plates. The m. p. varied with rate of the heating, but with a period of heating of 10—15 minutes a constant value of 264—265° (decomp., sealed) was obtained. For analysis it was dried at 15 mm. over potassium hydroxide (Found: C, 64·4; H, 5·9. $C_{13}H_{12}N_4,H_2O$ requires C, 64·4; H, 5·8%). Similar analytical figures were obtained for the *triaminoacridine* synthesised *via* the nitration of 5-aminoacridine. A mixed m. p. of the two preparations showed no depression, and both were insoluble in benzene, light petroleum, ether, or chloroform, slightly soluble in acetone, and moderately so in alcohol. The solubility in cold water was approximately 1 in 3000, and in hot water 1 in 900. Solutions in alcohol and water fluoresced green and darkened rapidly when exposed to the air. In ultra-violet light, solutions in concentrated hydrochloric acid showed a green-yellow fluorescence which changed first to brick-red and then to yellow, on addition of water.

3 : 5 : 7-Triaminoacridine formed a yellow *hydrochloride* which crystallised from dilute hydrochloric acid (Found: C, 42·4; H, 5·3; N, 14·8; Cl, 28·4. $C_{13}H_{13}N_4,3HCl,2H_2O$ requires C, 42·2; H, 5·2; N.

15·2; Cl, 28·8%). A similar analysis was obtained for the hydrochloride of the triaminoacridine synthesised *via* the nitration of 5-aminoacridine.

Hydrolysis of the Dinitro-5-aminoacridine from Nitration of 5-Aminoacridine.—The dinitro-5-aminoacridine (2 g.) was ground to a thin paste with water and added with stirring to boiling dilute sulphuric acid (1% v./v., 1 l.). After being heated under reflux for 3 hours, the mixture was cooled to 60° and the crystalline solid (1·94 g.) filtered off. This was obtained as yellow plates by the addition of hot water (980 ml.) to the hot solution in pyridine (420 ml.). Analysis showed the compound to be a *dinitroacridone* (Found: N, 14·6. $C_{13}H_7O_5N_3$ requires N, 14·7%).

3 : 7-*Diaminoacridone.*—3 : 7-Dinitroacridone (1 g.), obtained by nitration of acridone (Lehmstedt, *loc. cit.*, 1931), was heated under reflux for 3 hours with a solution of hydrated stannous chloride (6·2 g.) in concentrated hydrochloric acid (10 ml.). The mixture was cooled, and the hydrochloride filtered off and washed with cold concentrated hydrochloric acid. A solution of the salt in hot water was boiled with charcoal, and the base precipitated by addition of excess of ammonia. The product was extracted with boiling alcohol (150 ml.), and the filtrate after treatment with charcoal was concentrated to *ca.* 5 ml. Recrystallisation of the resulting crystals from alcohol gave orange prisms (0·42 g., 54%), m. p. 300—310° (decomp.; sealed). Bogert, Hirschfelder, and Lauffer (*Coll. Czech. Chem. Comm.*, 1930, **2**, 383) reported m p. 325° (corr.) for this compound. A mixed m. p. with the diaminoacridone obtained by a similar reduction of the dinitroacridone from the hydrolysis described above showed no depression (Found: C, 68·4; H, 5·2; N, 18·2. Calc. for $C_{13}H_{11}ON_3$: C, 69·3; H, 5·2; N, 18·7%). Similar analytical figures were obtained for the diamine synthesised *via* the hydrolysis of the dinitro-5-aminoacridine. Solutions of the compound in alcohol fluoresced strongly yellow-green in daylight, and in ultra-violet light solutions in dilute hydrochloric acid fluoresced a delicate rose-pink.

2 : 4 : 4′-*Trinitrodiphenylamine-2′-carboxylic Acid.*—(a) *By Ullmann condensation.* An intimate mixture of 5-nitroanthranilic acid (2 g.), 2 : 4-dinitrochlorobenzene (5·76 g.), anhydrous sodium carbonate (1·165 g.), and freshly precipitated copper (0·08 g.) was heated in an oil-bath at 200° for 30 minutes and then at 220—225° for 4 hours with occasional stirring. Ether (30 ml.) was added to the cooled mixture, the solid filtered off and extracted twice with boiling 1% sodium carbonate solution (250, 200 ml., respectively), and the combined extracts acidified at 70° with hydrochloric acid. The hot mixture was filtered, and the solid, after being washed with hot water, was dissolved in a boiling solution of sodium carbonate (0·28 g.) in water (200 ml.). The solution was treated with charcoal (0·2 g.), and 3N-sodium hydroxide (30 ml.) added to the hot filtrate. On cooling, the sodium salt separated as a red-brown gelatinous mass. After two recrystallisations from dilute sodium hydroxide, the salt was dissolved in water and the *carboxylic acid* precipitated with hydrochloric acid; yield, 0·38 g. (10%); m. p. 253°. It crystallised from glacial acetic acid as a yellow powder, m. p. 254—255° (Found: C, 44·4; H, 2·4; N, 16·0. $C_{13}H_8O_8N_4$ requires C, 44·8; H, 2·3; N, 16·1%).

(b) *By nitration of* 2 : 4-*dinitrodiphenylamine-2′-carboxylic acid.* This acid (Schroeter and Eisleb, *Annalen*, 1909, **367**, 101) (10 g.) was suspended in glacial acetic acid (200 ml.), concentrated nitric acid (2·5 ml., *d* 1·41) added, and the mixture brought to the boil. After gentle boiling for 15 minutes the solution was concentrated to *ca.* 20 ml. The bright yellow solid obtained on cooling was recrystallised from glacial acetic acid (charcoal); yield, 7·55 g. (66%); m. p. 254—255°. This substance did not depress the melting point of 2 : 4 : 4′-trinitrodiphenylamine-2′-carboxylic acid.

1 : 3 : 7-*Trinitroacridone.*—The foregoing acid (1 g.) was refluxed with phosphorus oxychloride (6 ml.) for 1·5 hours, and the solution cooled and poured with stirring on a mixture of ice and excess of ammonia. A slight excess of acetic acid was added, the mixture boiled for a few minutes and cooled, and the solid filtered off. This was ground under 4N-ammonia (250 ml.) at 40°, and the mixture cooled to room temperature and filtered from the insoluble ammonium salt of unchanged starting material. Neutralisation of the filtrate with concentrated hydrochloric acid yielded a pale-yellow crystalline solid which on recrystallisation from acetone (by concentration), using a mixture of kieselguhr and charcoal, gave yellow needles (0·25 g., 26%), m. p. 277° (Found: C, 46·9; H, 1·8; N, 16·8%). The m. p. was not depressed by the trinitroacridone from the nitration of 5-aminoacridine. Both these compounds were insoluble in water and benzene, slightly soluble in alcohol, moderately soluble in acetone, soluble in dilute ammonia.

A yellow by-product formed in the preparation of 3 : 7-dinitroacridone by nitration of 3-nitroacridone (19 g.) (Lehmstedt, *loc. cit.*, 1931) was found to be 1 : 3 : 7-trinitroacridone. The aqueous pyridine mother-liquors from the recrystallisation of 3 : 7-dinitroacridone were evaporated in a vacuum The residue (4·37 g.) was heated under reflux with glacial acetic acid (440 ml.) for 20 minutes, and the filtered extract, after being boiled with charcoal, deposited a yellow-brown solid (1·62 g.) on cooling. It was dissolved in glacial acetic acid, and the filtrate concentrated until solid separated. Recrystallisation from acetone as described above yielded bright yellow needles (0·9 g.), m. p. 277° (Found: C, 47·1; H, 1·8; N, 17·0%). A mixed m. p. with 1 : 3 : 7-trinitroacridone showed no depression.

5-*Chloro*-1-*nitroacridine.*—A mixture of 1-nitroacridone (Clemo, Perkin, and Robinson, *J.*, 1924, **125**, 1751) (10 g.), nitrobenzene (40 ml.), phosphorus oxychloride (35 ml.), and one drop of concentrated hydrochloric acid was heated in an oil-bath at 180° for 10 hours. After vacuum evaporation, the powdered residue was triturated with ice and excess of ammonia. The chloro-compound was filtered off, washed with ice-water and then alcohol, and dried in a vacuum; yield 10·3 g. (96%); m. p. 195—196°. Albert and Gledhill (*loc. cit.*, 1945) gave m. p. 195°. The product could be distilled at 12 mm. with slight decomposition; b. p. 265°.

1-*Nitro-5-aminoacridine.*—A stream of dry ammonia was passed for 4 hours through a solution of 5-chloro-1-nitroacridine (1 g.) in phenol (3·5 g.) kept in an oil-bath at 65°. Sodium hydroxide (3 g. in 40 ml. of water) was added to the cooled mixture, the precipitate collected and triturated with cold 2% acetic acid (30 ml.), and insoluble material filtered off and washed with more solvent. The combined filtrates on basification with sodium hydroxide yielded a bright red solid (0·71 g., 76%), m. p. 191—193°. Albert and Gledhill (*loc. cit.*, p. 1945) give m. p. 193°.

1 : 5-*Diaminoacridine.*—Finely powdered 1-nitro-5-aminoacridine (2 g.) was added gradually with mechanical stirring to a boiling solution of hydrated stannous chloride (7·3 g.) in concentrated hydro-

chloric acid (16 ml.), and the mixture heated on the water-bath for 1 hour. After cooling, sodium hydroxide (60 ml., 30%) was added, the precipitate filtered off and dissolved in 2% acetic acid (40 ml.), the solution clarified, and the base reprecipitated. Fractional precipitation with dilute sodium hydroxide from a solution of the crude base in 10% acetic acid (30 ml.) eventually yielded a yellow solid (0·83 g., 48%), m. p. 178°. The 1 : 5-*diaminoacridine* was obtained from aqueous acetone as yellow-brown crystals, m. p. 178—179° (Found: C, 74·0; H, 5·3; N, 20·0. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%); it was insoluble in water and benzene, easily soluble in acetone and alcohol. Solutions in alcohol and dilute hydrochloric acid fluoresced green.

4-*Nitro*-5-*aminoacridine*.—A mixture of 5-chloro-2- and -4-nitroacridines (9·74 g., Lehmstedt and Schrader, *loc. cit.*) was aminated in the manner described for 5-chloro-1-nitroacridine; crude yield, 5·98 g. The finely ground material was extracted twice with cold chloroform (900, 300 ml.), and the combined extracts were evaporated to dryness. The residue was dissolved in boiling benzene (550 ml.), and the solution filtered and concentrated to *ca.* 50 ml. The solid (3·1 g.), on recrystallisation from benzene (450 ml.) by concentration, gave red crystals of 4-nitro-5-aminoacridine (2·5 g.) (88% based on mixed chloro-compounds), m. p. 233—235°. Albert and Gledhill (*loc. cit.*, p. 1945) gave m. p. 234°.

4 : 5-*Diaminoacridine*.—Powdered 4-nitro-5-aminoacridine (1·25 g.) was stirred into a solution of ferrous sulphate crystals (9·7 g.) in water (35 ml.) at 75—80°. Precipitated chalk (3·2 g.) was added during 30 minutes at the same temperature, and the stirring continued at this temperature for a further hour, the mixture was brought to the boil and filtered, and the cake washed with boiling water (6 ml.). Red crystals of the sulphate which separated from the filtrate on cooling were dissolved in hot water (130 ml.), the solution clarified, cooled to 10°, and the base precipitated with N-sodium hydroxide. The product (0·8 g.) was extracted with boiling benzene (80 ml.), and the extract after treatment with charcoal and kieselguhr evaporated to dryness. The crystalline residue was dissolved in hot 0·1N-hydrochloric acid (10 ml.), the solution treated with charcoal, and concentrated hydrochloric acid (0·5 ml.) added; large orange-red crystals of the hydrochloride (0·61 g., 43%), m. p. 345° (decomp.), were obtained. Recrystallisation from dilute hydrochloric acid (charcoal) gave fine, silky, orange needles of the *monohydrochloride*, m. p. 346—347° (decomp.). For analysis it was dried at 25 mm. over calcium chloride (Found: C, 57·3; H, 5·6; N, 15·2; Cl, 13·3. $C_{13}H_{11}N_3$,HCl,1·5H_2O requires C, 57·2; H, 5·6; N, 15·4; Cl, 13·0%).

The *base* crystallised from benzene (by concentration) or benzene–light petroleum as orange needles, m. p. 147—148° (Found: C, 73·9; H, 5·4; N, 19·7. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). It was insoluble in water, moderately soluble in hot benzene, easily in acetone. Solutions in alcohol and dilute hydrochloric acid showed a weak green fluorescence.

All melting points given are uncorrected.

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214. *Epimeric Alcohols of the* cyclo*Hexane Series. Part VII. The 2-Methyl*cyclo*hexylcarbinols.*

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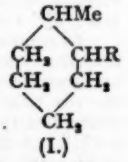
The epimeric forms of the racemic 2-methyl*cyclo*hexanecarboxylic acids and 2-methyl*cyclo*hexylcarbinols have been purified through and characterised by solid derivatives. Resolution of (±)-*trans*-2-methyl*cyclo*hexylcarbinol has been achieved through the (−)-*N*-menthylphthalamate.

IN continuance of the study of simple derivatives of *cyclo*hexane, the epimeric 2-methyl*cyclo*hexylcarbinols (I; R = CH_2·OH) have been prepared by the general methods used for 4-methyl*cyclo*hexylcarbinols (Cooke and Macbeth, *J.*, 1939, 1245). Reduction of *o*-toluic acid by catalytic hydrogenation over platinum in acetic acid, or over nickel in neutral aqueous solution, gave a liquid and a solid 2-methyl*cyclo*hexanecarboxylic acid (I; R = CO_2H), probably *cis*- and *trans*-, respectively. After purification these acids were converted into the ethyl esters which were converted into the epimeric carbinols (I; R = CH_2·OH) by hydrogenolysis over copper chromite.



(I.)

Compounds in the above series have been described previously, but without satisfactory evidence of purity for the liquids, as there has been no attempt at purification through solid derivatives. Markownikoff and Sernoff (*J. pr. Chem.*, 1894, **49**, 65), Goodwin and Perkin (*J.*, 1895, **67**, 119), Einhorn (*Annalen*, 1898, **300**, 156), Goldschmidt (*Chem.-Ztg.*, 1902, **26**, 335), and Skita (*Annalen*, 1923, **431**, 1) prepared a solid 2-methyl*cyclo*hexanecarboxylic acid, usually by reduction of *o*-toluic acid, and their results in general agree with ours, the m. p.s of the solid acid, its anilide, and its amide being 52°, 149°, and 183°, respectively.

For the liquid, or *cis*-, acid previously published results are unsatisfactory. The anilide has

been most often used for characterisation, and recorded m. p.s of this derivative are 68° by Goodwin and Perkin (*loc. cit.*)for an acid prepared from acyclic intermediates, 66° by Goldschmidt (*loc. cit.*), preparation from *o*-toluic acid, and 106° by Skita (*loc. cit.*), preparation from *cis*-2-methyl*cyclo*hexyl iodide. In the present research the liquid acid was purified through its solid *piperazine* salt, and the pure acid gave an anilide of m. p. 127°, depressed by the *trans*-anilide, but only to 105°. The amide of the pure *cis*-acid melted at 156°, agreeing closely with the data of Skita (*loc. cit.*) and Zelinsky (*Ber.*, 1908, **41**, 2680).

Skita (*loc. cit.*) described the preparation of the carbinols (I; R = CH_2·OH) by reduction of the methyl esters of the epimeric acids (I), but gave no evidence of homogeneity in the products. We found that esterification of the acids (I) and hydrogenolysis of the ester over copper chromite caused some inversion of configuration, and the crude carbinols needed extensive purification, which was rather difficult, as there was a marked tendency for solid derivatives to form mixed crystals with small amounts of the epimeric derivatives. Each of the crude hydrogen phthalates, and the 3 : 5-dinitrobenzoate of the crude *trans*-carbinol, resisted purification by crystallisation. Even after purification of the carbinols, several of their derivatives did not give very sharp m. p.s, and they showed the property of separating in different crystalline forms, apparently of slightly different m. p., depending on whether light petroleum or aqueous methyl alcohol was the solvent.

Attempts to resolve the acids (I; R = CO_2H) and the hydrogen phthalates of the carbinols (I; R = CH_2·OH) with several alkaloids were unsuccessful, for in no case was any separation of the diastereoisomeric mixtures observed. Eventually, the *trans*-carbinol was resolved as its (−)-*N*-menthylphthalamate, by the method of Human and Mills (*J.*, 1948, 1457), but the *cis*-carbinol was only partly resolved by this method.

Experimental.

The Racemic Epimeric Acids (I; R = CO_2H).—(*a*) Purified *o*-toluic acid (40 g.) was made up to a neutral solution in 9% aqueous sodium hydroxide (125 ml.), mixed with Raney nickel catalyst (4 ml.), and hydrogenated at 230—240° and 2500 lb. pressure, requiring 3—8 hours for complete hydrogenation. The crude *trans*-acid, recovered by filtration, acidification, ether extraction, and distillation under reduced pressure, was a pasty solid very soluble in all organic solvents. Contrary to the statement of Markownikoff and Sernoff (*loc. cit.*), it could not be recrystallised satisfactorily from benzene.

The crude acid (20·7 g.) was mixed with anhydrous piperazine (6·5 g., 1 equiv.) in dry acetone (65 ml.), and the solution boiled and cooled, yielding a crude salt (8·5 g.), m. p. 128—131°. The mother-liquors were used to convert more acid (24·9 g.) into the salt (36·3 g.), which was less pure, m. p. 112—125°. Recrystallisation from dry acetone in four fractions, the first fraction being recrystallised twice, the others four or five times, gave the pure *piperazine* salt (17 g.) as fine white needles, m. p. 135—136°, very soluble in alcohol and chloroform, sparingly in dry acetone, readily in moist acetone. Benzene and ethyl acetate were unsatisfactory solvents (Found: N, 7·5. $C_{20}H_{38}O_4N_2$ requires N, 7·6%).

The purified piperazine salt (16·5 g.) was shaken with 5% hydrochloric acid (60 ml.) and ether (50 ml.) for a short time, and the aqueous layer was separated and extracted with ether (20 ml.). The combined ethereal extracts were washed with water and dried, and the (±)-*trans*-2-methyl*cyclo*hexanecarboxylic acid recovered by distillation had b. p. 99°/2 mm., m. p. 51—52° (92% yield). This acid gave an anilide, fine scales from light petroleum, m. p. 148—149°; an amide, needles from light petroleum, m. p. 182—183°; and a *p-bromophenacyl* ester, needles from aqueous alcohol, m. p. 103—104° (Found: Br, 23·3. $C_{16}H_{19}O_3Br$ requires Br, 23·6%).

A sample of crude *trans*-acid was purified through the anilide, and the pure anilide was hydrolysed by refluxing with 70% sulphuric acid in an apparatus with a Dean and Stark attachment. The organic acid, which is volatile in steam, is thus recovered as fast as it is formed. The yield and purity (m. p. 47—51°) of the recovered acid were inferior to those from the purification as piperazine salt.

(*b*) Pure *o*-toluic acid (15 g.) was dissolved in glacial acetic acid (100 ml.) and hydrogenated over platinum oxide (0·5 g.) during 10 hours at 100° and atmospheric pressure. The hydrogenated acid, recovered by distilling the filtered solution under reduced pressure, was a liquid, which was combined with piperazine, giving a salt, m. p. 80—90°, in 75% yield. Recrystallisation from hot acetone (2 ml./g.) gave the pure *piperazine* salt in 88% recovery, as a crystalline powder, m. p. 96°, more soluble in all solvents than the corresponding *trans*-salt (Found: N, 7·6%). Decomposition of the pure salt yielded (+)-*cis*-2-methyl*cyclo*hexanecarboxylic acid, as a viscous liquid of mild, oily smell, b. p. 119/°11 mm., $d_4^{20°}$ 1·0159, $n_D^{20°}$ 1·4644.

To minimise the danger of epimerisation when preparing the anilide, the pure *cis*-acid was converted into the chloride by treating it in cold benzene solution with exactly one mole each of thionyl chloride and pyridine, and after 5 hours excess of aniline was added to the solution. The product recovered from the reaction was deep orange, but recrystallisation from dilute alcohol readily gave the pure *anilide* as white pearly plates, m. p. 126·5—127·5° (Found: C, 77·3; H, 8·9. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%). A mixed m. p. with the *trans*-anilide was observed under the microscope; there was no change at 66—68°, and the mixture melted at 105—115°. It was found that preparation of the *cis*-anilide by the method of Goodwin and Perkin (*loc. cit.*), involving a prolonged refluxing of the acid with aniline, gave a product, m. p. 112—115°, from which only a very small quantity of crude *cis*-anilide, m. p. 123—125° (identity shown by mixed m. p.), could be isolated. Evidently extensive epimerisation takes place.

The amide of the *cis*-acid was obtained as small scales from light petroleum, m. p. 155—156°, and the p-*bromophenacyl* ester as plates from aqueous alcohol, m. p. 81—82° (Found: Br, 23·6%).

The Racemic trans-*Carbinol* (I; R = CH_2·OH).—The pure *trans*-acid (52 g.) was dissolved in absolute

alcohol (500 ml.) with concentrated sulphuric acid (18 g.) and the mixture was slowly distilled through a column during 13 hours, water and alcohol (200 ml.) being collected. From the residual solution the ethyl ester was obtained in 97% yield as a liquid of rank and very persistent smell, b. p. 74°/11 mm., $d_4^{20°}$ 0·9272, $n_D^{16°}$ 1·4426.

The ester (20 g.) was mixed with copper chromite catalyst (2 g.) and shaken with hydrogen for 4 hours at 250° and 3000 lb. pressure. After removal of the catalyst, the crude carbinol was distilled; b. p. 80—81°/10 mm. (12·9 g., 90%).

The carbinol thus obtained was not stereochemically pure, and after unsuccessful attempts at purification through the hydrogen phthalate and 3 : 5-dinitrobenzoate, it was converted into the *p*-nitrobenzoate. The crude product obtained in 68% yield, had m. p. 42—44°, but four recrystallisations from 90—95% methyl alcohol gave half its weight as pure (±)-trans-2-*methyl*cyclo*hexylcarbinyl* p-*nitrobenzoate*, pale yellow plates, m. p. 59—60° (Found: C, 65·0; H, 6·9. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9%). Hydrolysis of this ester with 4% methyl-alcoholic caustic potash (1·25 moles) during one hour, and working up in the usual way, yielded (±)-*trans*-2-methyl*cyclo*hexylcarbinol, a viscous liquid, b. p. 80°/10 mm., $d_4^{26°}$ 0·9134, $n_D^{20°}$ 1·4633 (75% yield).

The pure *trans*-carbinol was converted into several esters: 3 : 5-*dinitrobenzoate*, small needles from light petroleum, m. p. 68·5—69·5° (Found: N, 8·7. $C_{15}H_{18}O_6N_2$ requires N, 8·7%); *phenylurethane*, triangular plates from light petroleum, m. p. 64—65°, or long needles from aqueous methyl alcohol, m. p. (partly) 59—60°, with second m. p. 63—64° (Found: N, 5·8. $C_{15}H_{21}O_2N$ requires N, 5·7%); *α-naphthylurethane*, needles from light petroleum, m. p. 87—88° (Found: C, 76·9; H, 8·1. $C_{19}H_{23}O_2N$ requires C, 76·7; H, 7·8%); *hydrogen phthalate*, crystalline powder from light petroleum, m. p. 98·5—99·5° (Found: C, 69·6; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%).

The Racemic cis-*Carbinol* (I; R = CH_2·OH).—The pure *cis*-acid was esterified by the method used for the *trans*-acid but with only two-thirds the quantity of sulphuric acid catalyst. The ethyl ester, obtained in 93% yield after distillation, had b. p. 76°/11 mm., $d_4^{20°}$ 0·9422, $n_D^{20°}$ 1·4472. Hydrogenation–hydrogenolysis was carried out as for the *trans*-ester. The crude *cis*-carbinol, which could not be purified through its hydrogen phthalate, was converted in 98% yield into a crude 3 : 5-dinitrobenzoate, m. p. 79—81°, and after three recrystallisations of this from methyl alcohol (10 ml./g.), three-fifths of it was recovered as pure (±)-cis-2-*methyl*cyclo*hexylcarbinyl* 3 : 5-*dinitrobenzoate*, small flat needles, m. p. 92—93° (Found: N, 8·7%). Hydrolysis with 4% methyl-alcoholic potash (1·5 moles) yielded (±)-*cis*-2-methyl-*cyclo*hexylcarbinol, b. p. 83°/10 mm., $d_4^{20°}$ 0·9286, $n_D^{20°}$ 1·4690 (80% yield).

From the pure *cis*-carbinol the following esters were made: p-*nitrobenzoate*, small plates from aqueous methyl alcohol, m. p. 43—44° (Found: C, 64·9; H, 6·8%); *phenylurethane*, stout rods from aqueous methyl alcohol, m. p. 47—48° (Found: N, 5·8%); *α-naphthylurethane*, small stout needles from light petroleum, m. p. 66—68° (Found: C, 76·9; H, 7·6%); *hydrogen phthalate*, minute needles from light petroleum, m. p. 112·5—114° (Found: C, 69·3; H, 7·1%).

Optical Resolution of (±)-trans-2-*Methyl*cyclo*hexylcarbinol*.—The hydrogen phthalate (50 g.) of this carbinol was dissolved in dry ether (600 ml.) and dry pyridine (14·3 g., 1 mole) was added; then to the refluxing solution thionyl chloride (13·0 ml., 1 mole) dissolved in ether (50 ml.) was added during one hour, with stirring. Refluxing was maintained for one hour longer, then a solution of (−)menthylamine (29·2 g., 1 mole) and pyridine (14·3 g.) in ether (100 ml.) was added during one hour. After a further 30 minutes' heating under reflux, the whole was set aside overnight. The crystalline precipitate of pyridine hydrochloride was dissolved in water, and the ethereal solution washed in turn with dilute hydrochloric acid, sodium carbonate solution, and water, and dried ($MgSO_4$). Removal of the ether left the diastereoisomeric mixture of esters as a yellow pasty solid (71 g., 95%).

Treatment of the crude product with light petroleum (b. p. 60—90°) left part of it undissolved as white needles, m. p. 102° (12·9 g.), and careful concentration of the light petroleum washings gave a further amount of similar material (15 g.). The two lots were mixed and recrystallised systematically in five fractions from aqueous methyl alcohol (80%, 25 ml./g.), and after five or six series of crystallisations pure (−)trans-2-*methyl*cyclo*hexylcarbinyl* (−)-N-*menthylphthalamate* (11 g.) was obtained as long needles, m. p. 109·5—110·5°, $[\alpha]_D^{16·5°}$ −39·7° (chloroform, *c* 5) (Found: N, 3·3. $C_{26}H_{39}O_3N$ requires N, 3·4%).

Hydrolysis of this ester was effected by refluxing for ½ hour with 8% methyl-alcoholic potash (1·3 moles), and after distillation of the bulk of the methyl alcohol, the residue was steam-distilled, and the steam-distillate submitted to continuous ether extraction. Removal of the ether left (−)*trans*-2-methyl*cyclo*hexylcarbinol, b. p. 73°/8 mm., $\alpha_D^{15·5°}$ −26·37° (homogeneous, *l* = 1), in 90% recovery, and 22% overall yield fron the (±)-carbinol.

The active carbinol was characterised by the preparation of the 3 : 5-*dinitrobenzoate*, fine needles from aqueous methyl alcohol, m. p. 48—50° (Found: N, 8·7%), and the *α-naphthylurethane*, fine needles from aqueous methyl alcohol, m. p. 104—104·5° (Found: N, 4·8%).

Attempted Resolution of (±)-cis-2-*Methyl*cyclo*hexylcarbinol*.—The (±)-*cis*-carbinol was converted into the (−)-*N*-methylphthalamic ester by the method used for the (±)-*trans*-carbinol. After a little oily material had been washed out with light petroleum (b. p. 40—60°), the diastereoisomeric mixture had m. p. 94—97°, $[\alpha]_D^{15·5°}$ −27·2° (chloroform, *c* = 5) (Found: N, 3·4%). Repeated recrystallisation from aqueous methyl alcohol altered these constants very little, so it is improbable that any appreciable resolution was achieved. Hydrolysis of the recrystallised ester yielded a carbinol with $\alpha_D^{14°}$ −1·66° (homogeneous, *l* = 1), a value which is much lower than is to be expected. This slightly active carbinol gave an α-naphthylurethane and a 3 : 5-dinitrobenzoate identical with those of the (±)-*cis*-carbinol.

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215. *The Chemistry of Simple Heterocyclic Systems. Part II. Condensations of 4-Chloro-6- and 4-Chloro-7-nitroquinazoline with Amines.*

By J. S. Morley and J. C. E. Simpson.

The condensation of 4-chloro-6- and -7-nitroquinazoline with a variety of primary aromatic and heterocyclic amines has been studied, and the results have been correlated with the basic strengths and nature of the amines. It has been established (i) that the chloro-compounds do not condense with primary heterocyclic amines in which a prototropic change to an imino-dihydro-derivative is formally possible, and (ii) that condensation occurs between the chloro-compounds and aromatic amines or *Bz*-heterocyclic amines provided that the pK_a values of such amines lie within the approximate range 1·0—5·2. Condensation does not occur if the pK_a values of the amines lie on either side of this range, and it is concluded that these results accord with the view that the reaction between chloro-heterocyclic compounds and amines is acid-catalysed.

During a study of the reactions of 6- and 7-nitro-4-hydroxyquinazoline and their derivatives (Morley and Simpson, *J.*, 1948, 2024), we observed that 4-chloro-6- and -7-nitroquinazoline readily condense with aniline in faintly acid aqueous medium, these conditions being chosen as they had previously been found to be well suited for the production of arylamino-heterocyclic derivatives (cf. Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127, 1131; Banks, Gruhzit, Tillitson, and Controulis, *ibid.*, 1944, **66**, 1771; Andres and Hamilton, *ibid.*, 1945, **67**, 946; Tomisek and Christensen, *ibid.*, 1945, **67**, 2112; Banks and Controulis, *ibid.*, 1946, **68**, 944; Curd and Rose, *J.*, 1946, 343; Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370). Subsequently it was found that, if 2 : 4-dinitroaniline be substituted for aniline, no reaction occurs, apart from hydrolysis of the chloro- to the hydroxy-quinazolines. This lack of reaction between a weak base and the chloronitroquinazolines seemed of particular interest inasmuch as failures have also been reported for the much more strongly basic dialkylaminoalkylamines (Banks, *loc. cit.*; Curd and Rose, *loc. cit.*), in contrast with the rapid reactions, already referred to, which occur between chloroheterocyclic compounds and amines of intermediate basicity (aniline, *p*-chloroaniline, etc.). Accordingly we have studied the reactivity, in slightly acid aqueous acetone, between 4-chloro-6- and -7-nitroquinazoline and a representative range of amines. In addition to the failure with 2 : 4-dinitroaniline, negative results were also obtained with 1-nitro-2-naphthylamine, benzylamine, 4-amino- and 6-nitro-4-amino-quinoline, 4-amino-, 6-chloro-4-amino-, and 6-nitro-4-amino-cinnoline, 6-nitro-4-aminoquinazoline, and 2-amino-pyridine; in nearly all these cases the non-occurrence of condensation was demonstrated by the isolation of the chloro- or hydroxy-quinazoline, and sometimes by that of the amine also. On the other hand, reaction occurred rapidly between the chloro-compounds and (in addition to aniline) *m*- and *p*-nitroaniline, *p*-anisidine, diaminouracil, 5- and 6-aminoquinoline, and 3-amino-6-methylquinoline, leading to the formation of 6- and 7-*nitro*-4-m- and -p-*nitroanilino*-, -4-p-*anisidino*-, -4-(4′-*amino*-2′ : 6′-*dihydroxy*-5′-*pyrimidylamino*)-, -4-5′- and -4-6′-*quinolylamino*-, and -4-6′-*methyl*-3′-*quinolylamino*-*quinazoline*.

Comparison of these results with published data revealed that the group of non-reacting amines contained bases both stronger and weaker than those which react; *e.g.*, 4-aminoquinoline (does not condense), pK_a 8·46 (Albert and Goldacre, *Nature*, 1944, **153**, 467); aniline (condenses) pK_a 4·7 (Waters, "Physical Aspects of Organic Chemistry," Routledge, 1937, p. 208; Handbook of Chemistry and Physics, Chemical Rubber Publishing Co., 1944); 2 : 4-dinitroaniline (does not condense), pK_a −4·38 (Glasstone, "Introduction to Electrochemistry," New York, 1942).

In order to throw further light on the possible relations between the basicity of an amine and its ability to react with the chloronitroquinazolines under the particular conditions used, we have determined, as indicated in Table I, the pK_a values of the bases studied in this investigation, in cases where these were lacking. In this table the bases are listed in decreasing order of basic strength, with the proviso that the "second pK_a" value (pK_{a_2}), if shown, takes precedence over the "first pK_a" value (pK_{a_1}) in determining the order of placing; they are also divided into reactive and unreactive groups. The positions of 1-nitro-2-naphthylamine in the Table is uncertain, as, owing to its weak basicity, it was not possible to determine its pK_a value even approximately under the conditions used.

The significance of the "second pK_a" values calls for some explanation. In the case of diaminouracil the determination was made by acid titration of the sulphate (B_2,H_2SO_4; Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667) and is therefore probably an estimation of pK_{a_2}, which, for reasons of the kind discussed by Albert and Goldacre (*loc. cit.*), may be

considered to be that of the " aromatic " amino-group of this compound. With 5- and 6-aminoquinoline, potentiometric titrations were made on the free bases, and thus gave pK_{a_1} values. The question therefore arose as to whether these values are related to the ring-nitrogen or to the

TABLE I.

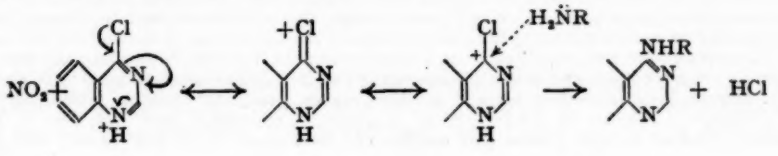
Non-reactive amines.	Solvent.*	Temp.	Ref.	pK_{a_1}.	pK_{a_2}.	Reactive amines.
			4	9·4	—	—
Benzylamine	A	24—25°	1	8·9	—	—
	B	24—25	1	9·2	—	—
4-Aminoquinoline	A	24—25	1, 2	8·45	—	—
2-Aminopyridine	—	—	3	6·85	—	—
			2	7·15	—	—
6-Nitro-4-aminoquinoline ...	A	24—25	1	6·4	—	—
4-Aminocinnoline	A	24—25	1	6·25	—	—
6-Chloro-4-aminocinnoline	A	28	1	5·4	—	—
			4	5·15	—	*p*-Anisidine
6-Nitro-4-aminocinnoline ...	A	24—25	1	5·1	—	—
			5	4·7	—	Aniline
	[A	24—25	1	4·25	—	† 3-Amino-6-methylquinoline]
6-Nitro-4-aminoquinazoline	A	24—25	1	3·7	—	—
			6	2·6	—	*m*-Nitroaniline
	A	24—25	1	—	1·7	Diaminouracil
			2	5·6	1·60 ‡	6-Aminoquinoline
			7	1·1	—	*p*-Nitroaniline
			2	5·5	0·96 ‡	5-Aminoquinoline
[1-Nitro-2-naphthylamine]						
2 : 4-Dinitroaniline	—	—	7	−4·38	—	—

* A = 50% aqueous alcohol. B = water.
† Morley and Simpson, *J.*, 1948, 2024.
‡ Spectrographic determination at 20°; private communication from Professor R. A. Morton.

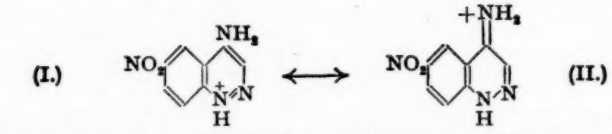
1. This paper. 2. Albert and Goldacre (*loc. cit.*) (in water at 20°). 3. Tropsch, *Monatsh.*, 1914, **35**, 775. 4. Heilbron's " Dictionary of Organic Compounds " (1st Edition). 5. Mean values from Heilbron, Waters, and " Handbook of Chemistry and Physics " (*opp. cit.*). 6. Mean values from Heilbron and Waters (*opp. cit.*). 7. Glasstone, " Introduction to Electrochemistry," New York, 1942.

primary amino-group. From a spectrographic study of the aminoacridines, Craig and Short (*J.*, 1945, 419) concluded that the formation of salts of these bases involves the addition of the first proton to the ring-nitrogen, and Irvin and Irvin (*J. Amer. Chem. Soc.*, 1947, **69**, 1091) state that this is probably true also of various 4-aminoquinolines. Professor R. A. Morton has kindly investigated the absorption spectra of 5- and 6-aminoquinoline in acid solution, and has informed us that, in these compounds also, the first proton is in all probability accepted by the ring-nitrogen. The basicities of the amino-groups of these compounds are therefore indicated by the pK_{a_2} values, which were calculated from the spectrographic data. (3-Amino-6-methylquinoline was not examined spectrographically, and its exact position in the Table is therefore uncertain, but a similar state of affairs no doubt holds good also in this case).

It will be seen from Table I that the pK_a values of amines which react with the chloronitroquinazolines fall within a limited range (in the definition of which pKa_2 again takes precedence over pK_{a_1}), the extreme values of the examples studied being 5·15 and 0·96, and that the reaction does not occur with amines of which the pK_a values lie on either side of this range. This is precisely the behaviour which would be expected if, as suggested by Banks, by Andres and Hamilton, and by Banks and Controulis (*locc. cit.*), the reaction between amines and chloro-heterocyclic compounds is acid-catalysed; for, according to the amount by which the basicity of the primary amine exceeds that of the heterocyclic chloro-compound, the share of the available protons acquired by the latter will be correspondingly smaller and the condensation consequently inhibited (Case A); on the other hand, a reduction in basicity of the primary amine will diminish proportionately its power of co-ordination with the kationoid C_4 (see below), and ultimately a point will be reached beyond which the anionoid attack on the chloro-heterocyclic compound is no longer possible (Case B).



Further reference to Table I shows that in no case does a compound containing a " heterocyclic " amino-group (*i.e.*, an amino-group attached to C_2 or C_4 of the heterocyclic ring) react with the chloro-compounds, even if the pK_{a_1} value of the amino-compound falls within the " active " range, as with 6-nitro-4-amino-cinnoline and -quinazoline. This lack of reactivity is without doubt due to the fact that the monokations are greatly stabilised by resonance [*e.g.*, forms (I) and (II) for 6-nitro-4-aminocinnoline] of the type discussed for 4-aminoquinoline



by Albert and Goldacre (*loc. cit.*), and pK_{a_1} for such compounds therefore falls below the lower critical limit (Case B). In the case of 4-amino-heterocyclic compounds of high pK_{a_1} values, the conditions of Case A could also operate.

After this work was completed, a note by Meyer and Bouchet (*Compt. rend.*, 1947, **225**, 63) appeared, in which the condensation of 4-chloroquinaldine with various amines (usually in acetic acid–sodium acetate) was described. Their results, although only of a qualitative character, are in general agreement with our own; thus these authors conclude that the reaction depends on the basicity of the amine used, and that it is successful with diazotisable amines, but fails with tautomerisable amino-heterocyclic compounds.

Experimental.

Melting points are uncorrected.

The experiments shown in Table II were carried out by heating under reflux for ½ hour a mixture of 4-chloro-6- or -7-nitroquinazoline (usually 0·4 g.) and the appropriate amine (5—10% excess) in 50% aqueous acetone (usually 20 c.c.) containing 2—3 drops of concentrated hydrochloric acid. It was

Table II.

		Products isolated from attempted condensation with 4-chloro-6-nitro-quinazoline.			Products isolated from attempted condensation with 4-chloro-7-nitro-quinazoline.		
Expt. no.	Amine.	Chloro-quinazo-line.	Hydroxy-quinazo-line.	Amine.	Chloro-quinazo-line.	Hydroxy-quinazo-line.	Amine.
1.	2 : 4-Dinitroaniline	−	+	+	−	+	+
2.	1-Nitro-2-naphthylamine	−	+	+	−	+	+
3.	6-Nitro-4-aminoquinazoline [1]	−	+	+	−	+	+
4.	6-Chloro-4-aminocinnoline [2] ...	−	+	+	−	+	+
5.	6-Nitro-4-aminoquinoline [3] ...	−	+	+	−	+	+
6.	4-Aminocinnoline [2,4]	−	+	+	−	+	+
7.	Benzylamine [4]	−	+		+	−	
8.	4-Aminoquinoline	+	−	+	+	−	+
9.	2-Aminopyridine	+	−		+	−	
10.	6-Nitro-4-amino-cinnoline [2] ...			+			+

[1] Morley and Simpson, *J.*, 1948, 360.
[2] Keneford, Schofield, and Simpson, *J.*, 1948, 358.
[3] Simpson and Wright, *J.*, 1948, 1707.
[4] In these experiments complete separation and identification of the total reaction product was not achieved. A blank space in the Table indicates that no search was made for the compound in question.

observed that the pH of the reaction medium was *ca.* 7 in those experiments in which the chloro-compounds were recovered; if the pH was appreciably (*ca.* 1 unit or more) on either side of the neutral point, hydrolysis of the chloro- to the hydroxy-quinazoline resulted. The chloroquinazolines separated directly from the hot solution after removal of acetone, and the hydroxyquinazolines and amines were isolated by utilising their respective solubilities in alkali and acid; the yields of products were *ca.* 80—90%.

Preparation of 6- *and* 7-*Nitro*-4-*arylaminoquinazolines.*—The following compounds were prepared from the appropriate chloroquinazoline and amine under the conditions used for the experiments listed above; at the end of each reaction (½ hour under reflux) the suspension was basified with ammonia, and the resultant amines were recrystallised from suitable solvents (referred to numerically below) as follow: (1) acetic acid; (2) aqueous acetic acid; (3) aqueous pyridine; (4) aqueous alcohol; (5) absolute alcohol. 6-*Nitro*-4-m-*nitroanilinoquinazoline* formed brittle, yellow prismatic needles (yield, 85%) (1), m. p. 270—271° (Found: C, 53·75; H, 3·1; N, 22·1. $C_{14}H_9O_4N_5$ requires C, 54·0; H, 2·9; N, 22·5%). The 7-*nitro*-isomer, clusters of pale yellow soft needles (1), had m. p. 284—285° (yield, 83%) (Found: C,

52·6; H, 3·1; N, 22·2. $C_{14}H_9O_4N_5,\frac{1}{2}H_2O$ requires C, 52·5; H, 3·1; N, 21·9%). 6-*Nitro*-4-p-*nitroanilinoquinazoline*, m. p. 319—320° (decomp.), formed bright yellow, fluffy needles (2) (yield, 98%) (Found: C, 54·4; H, 3·05; N, 22·8. $C_{14}H_9O_4N_5$ requires C, 54·0; H, 2·9; N, 22·5%). The 7-*nitro*-isomer separated (1 or 2) in stout, yellow, brittle needles, m. p. 291—292° (decomp.) (yield, 95%) (Found: C, 53·9; H, 3·0; N, 22·3%). 6-*Nitro*-4-6′-*methyl*-3′-*quinolylaminoquinazoline* crystallised (1) in warts of fine, deep yellow needles, m. p. 294—295° (yield, 100%) (Found: C, 65·8; H, 3·9; N, 20·8. $C_{18}H_{13}O_2N_5$ requires C, 65·25; H, 3·95; N, 21·1%). The 7-*nitro*-isomer (yield, 100%), m. p. 337—338° (decomp.), formed bright yellow, feathery needles (1) (Found: C, 64·8; H, 3·8; N, 20·9%). The product from 4-chloro-6-nitroquinazoline and 4 : 5-diamino-2 : 6-dihydroxypyrimidine separated as a pale orange solid when the reaction mixture was brought to pH 7; it did not melt at 340°, and was not purified (yield, 76%). 7-*Nitro*-4-4′-*amino*-2′ : 6′-*dihydroxy*-5′-*pyrimidylaminoquinazoline* was isolated similarly (yield, 81%), and was purified by dissolution in 0·25N-sodium hydroxide, cautious acidification, and recrystallisation (3); it formed orange micro-crystals, which did not melt at 340° (Found: C, 44·3; H, 3·7; N, 29·2. $C_{12}H_9O_4N_7,\frac{1}{2}H_2O$ requires C, 44·4; H, 3·1; N, 30·2%). 6-*Nitro*-4-p-*anisidinoquinazoline* (yield, 100%) crystallised in soft orange needles (4) or dense, bright red prisms (5), m. p. 203—205° (Found: C, 60·5; H, 3·8; N, 19·2. $C_{15}H_{12}O_3N_4$ requires C, 60·8; H, 4·1; N, 18·9%). The 7-*nitro*-isomer (yield, 100%) formed soft maroon needles (5), m. p. 236—238° (Found: C, 60·5; H, 4·1; N, 19·0%). 6-*Nitro*-4-5′-*quinolylaminoquinazoline* (96% yield), m. p. 282—283° (decomp.), formed soft buff-coloured needles (4) (Found: C, 61·2; H, 3·6; N, 20·8. $C_{17}H_{11}O_2N_5,H_2O$ requires C, 60·9; H, 3·9; N, 20·9%). The 7-*nitro*-isomer (95% yield) had m. p. 301—302° (decomp.), and crystallised as yellow needles (2) (Found: C, 63·95; H, 3·5; N, 22·2. $C_{17}H_{11}O_2N_5$ requires C, 64·3; H, 3·5; N, 22·1%). 6-*Nitro*-4-6′-*quinolylaminoquinazoline* (83% yield), clusters of minute yellow needles (1), had m. p. 333—335° (decomp.) (Found: C, 64·2; H, 3·5; N, 22·4. $C_{17}H_{11}O_2N_5$ requires C, 64·3; H, 3·5; N, 22·1%). 7-*Nitro*-4-6′-*quinolylaminoquinazoline dihydrochloride* (yield, 72%) crystallised from N-hydrochloric acid in pale yellow needles, m. p. 319—320° (decomp.) (Found: C, 50·5; H, 3·7; N, 17·0. $C_{17}H_{11}O_2N_5,2HCl,H_2O$ requires C, 50·0; H, 3·7; N, 17·1%).

A characteristic reaction of the arylaminoquinazolines was the production of a deep-red colour on treatment with dilute aqueous–alcoholic alkali.

Determination of pK_a *Values.*—The determinations were carried out by means of a Cambridge portable pH meter, mechanically-stirred solutions of the bases (30—40 mg.) in 50% aqueous alcohol (50 c.c.) being titrated with 0·1N-aqueous hydrochloric acid at 24—25°; the pK_a values were read from the titration curves at half-neutralisation points. For values of 4 and over, the results given in Table I are uncorrected. For values below 4, *i.e.*, where the observed curve gradually approaches the blank (acid dilution) curve as the basicity diminishes, corrected pK_a values were obtained from the equation (Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405)

$$pK_a = pH + \log\frac{c/2 - [H^+]}{c/2 + [H^+]},$$

where c = initial concentration of base, and the values of pH and $[H^+]$ are those at the calculated half-neutralisation point. This equation gives a correction for the error introduced into a straightforward pK_a determination by the hydrolysis of the salt when the base is weak. For a given concentration and below a certain pH value, however, the magnitude of the correction (the second term on the right-hand side) increases very rapidly with small decreases in pH. There is thus a lower critical limit of observed pK_a value (about 2·7 in our experiments) below which the " corrected " values have no real quantitative significance; for this reason the value for diaminouracil sulphate is only very approximate, and no result of any significance could be obtained for 1-nitro-2-naphthylamine.

It is a pleasure to record our indebtedness to Dr. A. Hickling for helpful discussions and advice on the determination and significance of pK_a values, and to the Medical Research Council for a Research Studentship (J. S. M.).

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216. *Attempts to find New Antimalarials. Part XXVIII.* p-*Phenanthroline Derivatives substituted in the* 4-*Position.*

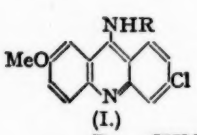
By BRYCE DOUGLAS and WILLIAM O. KERMACK.

The ethyl ethoxymethylenemalonate method has been employed for the synthesis of 4-chloro-, 4 : 9-dichloro-, and 4 : 5-dichloro-*p*-phenanthroline. In the first two of these, the chlorine atom has been replaced by a basic side chain, and the resulting compounds exhibit considerable activity against *P. gallinaceum* in chicks. The base obtained from 4 : 5-dichloro-*p*-phenanthroline and 3-diethylaminopropylamine is probably 4 : 5-(3′-diethylaminopropylimino)-*p*-phenanthroline (VIII). The relation of the active *p*-phenanthroline compounds to the antimalarials of the mepacrine, chloroquine, and benz- and pyridino-acridine classes is discussed.

IT has been shown that when a pyridine ring is fsued on to a compound of the mepacrine type (I) so as to form a derivative of pyridino-3 : 4 : 2′ : 3′-acridine (II), the resulting base shows antimalarial activity (*J.*, 1946, 150; 1947, 678; 1948, 123). The activity of mepacrine is very

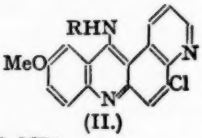
much reduced if the chlorine atom in position 2 is removed. Similarly, the pyridinoacridine derivatives are fairly highly active if they contain a chlorine atom in position 2 or 8, or in both positions, but retain only feeble activity when devoid of chlorine atoms.

It will be observed that all the more active compounds referred to above, including mepacrine itself, are derivatives of the very highly active chloroquine type (III); that is, they can be regarded as derived from 4-dialkylaminoalkylamino-7-chloroquinoline. These facts suggest that in this class of antimalarial compound, the chloroquine structure has some basic significance. Now, it is to be observed that in the active pyridoacridine compound, we may remove the benzene ring and still retain the chloroquine structure. In this way, in fact, we reach a derivative of *p*-phenanthroline of the type (IV). Such a *p*-phenanthroline derivative may be regarded as formed by the fusion of a pyridine ring to chloroquine; thus (IV) bears much the same relation to chloroquine as the active pyridinoacridines do to mepacrine.

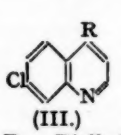


(I.)

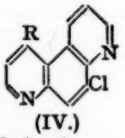
R = ·CHMe·[CH$_2$]$_3$·NEt$_2$·



(II.)



(III.)



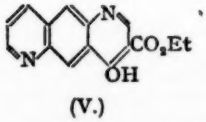
(IV.)

R = Dialkylaminoalkylamino-.

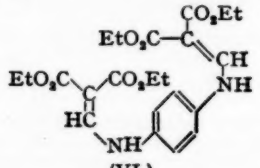
Kermack and Weatherhead (*J.*, 1940, 1164) have synthesised a number of *p*-phenanthroline derivatives carrying a basic group in the 4-position, including 4-(3′-diethylaminopropylamino)-*p*-phenanthroline and 4-(3′-diethylaminopropylamino)-2-methyl-*p*-phenanthroline; both these compounds proved inactive when tested on *P. relictum* in canaries. However, in view of the above considerations it was desirable to test similar derivatives of *p*-phenanthroline or analogous derivatives carrying a chlorine atom in position 9. The opportunity was also taken to synthesise 4-chloro-*p*-phenanthroline by a new route and to prepare 4-(*4′-diethylamino-1′-methylbutylamino*)-p-*phenanthroline* in the hope that even in the absence of a chlorine atom the more chemotherapeutically active *iso*amyl side chain might confer some antimalarial activity on these *p*-phenanthroline derivatives.

Ethyl ethoxymethylenemalonate condensed smoothly with 6-aminoquinoline to yield *ethyl* β-(*6′-quinolylamino*)-α-*carbethoxyacrylate*, which when heated in mineral oil afforded 4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline* in good yield. The possibility that the cyclised product might be the isomeric linear diaza-anthracene derivative (V) and not the angular *p*-phenanthroline was excluded by the fact that when the ester was hydrolysed to the acid, and the latter decarboxylated, the product was 4-hydroxy-*p*-phenanthroline, already prepared by a different route (Kermack and Weatherhead, *loc. cit.*) and converted by these authors into *p*-phenanthroline by zinc dust distillation. It is useful to have this confirmation of the expected angular cyclisation of ethyl β-(6′-quinolylamino)-α-carbethoxyacrylate.

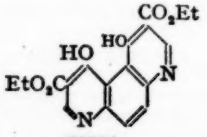
Ethyl ethoxymethylenemalonate condensed readily with 8-chloro-6-aminoquinoline to yield *ethyl* β-(*8′-chloro-6′-quinolylamino*)-α-*carbethoxyacrylate*. This compound cyclised in mineral oil to yield an ester, which on analogy with the results of the previous paragraph may confidently be assumed to be 9-*chloro*-4-*hydroxy*-3-*carbethoxy*-p-*phenanthroline*. The corresponding acid, on decarboxylation, affords 9-*chloro*-4-*hydroxy*-p-*phenanthroline*, which on treatment with phosphoryl chloride and phosphorus pentachloride is converted into 4 : 9-*dichloro*-p-*phenanthroline*.



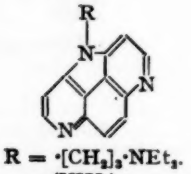
(V.)



(VI.)



(VII.)



R = ·[CH$_2$]$_3$·NEt$_2$.

(VIII.)

It was thought of interest to examine the reaction of *p*-phenylenediamine with ethyl ethoxymethylenemalonate in order to ascertain whether *p*-phenanthroline derivatives could be obtained by means of a double cyclisation of the intermediate NN′-*bis*-(2 : 2-*dicarbethoxyvinyl*)-p-*phenylenediamine* (VI). This compound was readily formed from 1 mol. of *p*-phenylenediamine and 2 mols. of ethyl ethoxymethylenemalonate, and though it did not yield the *p*-phenanthroline derivative (VII) when heated in paraffin at 250°, the double cyclisation proceeded satisfactorily in boiling diphenyl. The isolation of the intermediate compound

was unnecessary: an excellent overall yield was obtained by adding the *p*-phenylenediamine and ethyl ethoxymethylenemalonate to diphenyl and heating them under reflux for 45 minutes. Hydrolysis of the resulting ester afforded 4 : 5-*dihydroxy*-3 : 6-*dicarboxy*-p-*phenanthroline* which was decarboxylated to 4 : 5-*dihydroxy*-p-*phenanthroline*. Treatment of the latter with phosphoryl chloride and phosphorus pentachloride gave 4 : 5-*dichloro*-p-*phenanthroline*.

The *p*-phenanthrolinecarboxylic acids were difficult to purify, and it was observed that if the acids were contaminated with the sodium salts, decarboxylation, which was usually effected by heating in boiling quinoline in presence of a little copper chromite, was seriously inhibited. It was therefore necessary to ensure the purity of the acids from these contaminants. A similar observation is recorded by Lauer (*J. Amer. Chem. Soc.*, 1946, **68**, 1268) in connection with the decarboxylation of 6-chloro-4-hydroxy-3-carboxy-8-methoxyquinoline.

4-Chloro- and 4 : 9-dichloro-*p*-phenanthroline were heated with the appropriate amines to yield 4-(4′-*diethylamino*-1′-*methylbutylamino*)- and 9-*chloro*-4-(3′-*diethylaminopropylamino*)-p-*phenanthroline*. Salts of these bases with hydrochloric, hydrobromic, and various organic acids were prepared but the products, although crystalline solids, were deliquescent and became sticky on standing. For purification and analysis, the 3 : 5-dinitrobenzoates were most satisfactory, being crystalline and non-deliquescent. When 4 : 5-dichloro-*p*-phenanthroline was heated with a large excess of diethylaminopropylamine an oily base was obtained which yielded deliquescent salts with most acids but formed a crystalline *bis*-3 : 5-*dinitrobenzoate*. Analysis indicated that only one diethylaminopropylamino-group had reacted with 1 mol. of 4 : 5-dichloro-*p*-phenanthroline to yield a chlorine-free product, which probably has the structure (VIII). The failure of two separate diethylaminopropylamino-groups to attach themselves to the 4- and the 5-position of the *p*-phenanthroline nucleus may be due to steric hindrance between the two nitrogen atoms each with its attached diethylaminopropylamino-groups.

We are indebted to Dr. W. L. M. Perry of the National Institute for Medical Research for the reports on the antimalarial activity of 4-(4′-diethylamino-1′-methylbutylamino)- and 9-chloro-4-(3′-diethylaminopropylamino)-*p*-phenanthroline. These compounds have been tested against *P. gallinaceum* in chicks with the following results (bd × 4 indicates dose given twice daily for the first 4 days; D = died; K = killed):

9-*Chloro*-4-(3′-*diethylaminopropylamino*)-p-*phenanthroline*.

	Day after infection, and % parasitæmia.														
Dosage.	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10 Mg./20 g. ...	—	—	—	—	—	—	—	—	—	<1	1	5			
bd × 4	—	—	—	—	—	—	—	<1	2	50	K				
Nil	20	25	30	D											
	—	—	2	10	80	D									
	—	—	1	5	15	D									
	—	—	1	5	8	D									

4-(4′-*Diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline*.

	Day after infection, and % parasitæmia.															
Dosage.	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10 Mg./20 g. ...	—	—	—	—	<1	1	2	5	5	10	50	70	D			
bd × 4	—	—	—	—	—	—	—	<1	1	1	2	5	10	50	80	D
Nil	—	—	—	1	5	10	30	60	80	D						
	—	<1	1	5	10	20	10	10	50	70	D					
	—	—	—	—	1	1	2	10	50	D						
	—	—	—	—	1	2	5	30	50	70	80	D				

Repeat test with 4-(4′-*diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline*.

	Day after infection, and % parasitæmia.														
Dosage.	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10 Mg./20 g. ...	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
bd × 4	—	—	—	—	—	—	—	—	—	1	5	50	D		
5 Mg./20 g.	—	—	—	—	—	—	—	<1	1	5	70	D			
bd × 4	—	—	—	<1	2	5	10	50	60	70	D				
Oral	—	—	—	—	1	10	20	70	D						
Nil	20	25	30	70	D										
	—	—	2	30	80	D									
	—	—	1	5	15	70	D								
	—	—	1	2	8	50	D								

Both compounds produced a considerable delay in the appearance of the parasites in the blood in doses of 10 mg./20 g. of body weight. The data do not allow exact comparison of the activities of these compounds with those of standard antimalarials, such as mepacrine or quinine, but they would seem to be of the same order.

The considerable activity of the second compound on *P. gallinaceum* is in accordance with the general considerations developed above. It will be seen that the compound with the *iso*amyl side chain but without the chlorine atom was also moderately active in contrast with the lack of activity of the 4-(3′-diethylaminopropylamino)-*p*-phenanthroline when tested on *P. relictum* in canaries. Further tests with this compound on *P. gallinaceum* in chicks will be required to decide if the marked contrast in activity is due to the different side chains or to a difference in susceptibility of the two species of the parasite.

Experimental.

Ethyl β-(6′-Quinolylamino)-α-carbethoxyacrylate.—6-Aminoquinoline (1 g.) and ethyl ethoxymethylenemalonate (2 c.c.) were heated under reduced pressure at 100° on the water-bath for 45 minutes to give a brown syrup which solidified on cooling; this was collected, drained, washed with light petroleum (b. p. 60—80°), and dried to give a white solid (2 g., m. p. 88—90°) which on recrystallisation from ethanol yielded large white rectangular plates, m. p. 97—98°, of *ethyl β-(6′-quinolylamino)-α-carbethoxyacrylate* (Found: C, 65·1; H, 5·7; N, 8·8. $C_{17}H_{18}O_4N_2$ requires C, 65·0; H, 5·7; N, 8·9%).

*4-Hydroxy-3-carbethoxy-*p*-phenanthroline.*—The foregoing ester (9 g., m. p. 88—90°) was added in small portions during 15 minutes to mineral oil (180 c.c.), preheated to 250—260°. Yellowish-brown solid was collected from the cooled oil, drained, washed with light petroleum (b. p. 60—80°), and dried to give a brown solid (7·0 g., m. p. 265—270°) which was recrystallised from ethanol (charcoal), yielding colourless rectangular prisms, m. p. 285—286°, of *4-hydroxy-3-carbethoxy-*p*-phenanthroline* (Found: C, 66·9; H, 4·6; N, 10·2. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5; N, 10·45%).

*4-Hydroxy-3-carboxy-*p*-phenanthroline.*—The carbethoxy-compound (16 g., m. p. 265—270°) was heated under reflux with 20% methanolic potassium hydroxide (160 c.c.) for 6 hours. Water (350 c.c.) was added, and the dark brownish-red solution treated with charcoal, filtered, and made acid with glacial acetic acid. The deposited cream solid was collected, drained, washed with water, and dried (13 g., m. p. 270—280° with frothing). This product was dissolved in 2N-ammonium hydroxide, treated with charcoal, filtered, and reprecipitated with 2N-acetic acid to yield, after three treatments, cream micro-needles, m. p. 307—308° with frothing, of *4-hydroxy-3-carboxy-*p*-phenanthroline* (Found: C, 60·4; H, 4·2; N, 10·4. $C_{13}H_8O_3N_2,H_2O$ requires C, 60·5; H, 3·9; N, 10·85%).

*4-Hydroxy-*p*-phenanthroline.*—(A) The preceding acid (11 g., m. p. 270—280° with frothing), copper–barium chromite catalyst (Connor, Folkers, and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 1138) (0·1 g.), and dry redistilled quinoline (220 c.c.) were heated under reflux for 45 minutes. The mixture, cooled to 100°, was filtered, and the filtrate steam-distilled to remove the quinoline. The resulting aqueous solution was evaporated to dryness to yield a brown solid (8 g., m. p. 275—280°) which, recrystallised from boiling water (charcoal), yielded pale yellow fibrous needles, m. p. 300—301°, of 4-hydroxy-*p*-phenanthroline; the mixed m. p. with a sample prepared by the method of Kermack and Weatherhead (*loc. cit.*) was 299—300° (Found: C, 68·5; H, 4·2; N, 13·15. Calc. for $C_{12}H_8ON_2,\frac{1}{2}H_2O$: C, 68·7; H, 4·5; N, 13·4%).

(B) 4-Hydroxy-3-carboxy-*p*-phenanthroline (1 g., m. p. 270—280° with frothing) was heated at 300° in a dry test-tube until frothing ceased, to yield a solid black residue (0·7 g.) which was extracted with boiling water (3 × 50 c.c.) and the combined extracts concentrated (30 c.c.) to yield yellow needles, m. p. 298—300°, which crystallised from water in pale yellow fibrous needles, m. p. 300—301°, of 4-hydroxy-*p*-phenanthroline.

*4-Chloro-*p*-phenanthroline.*—4-Hydroxy-*p*-phenanthroline (5 g., m. p. 300—302°), phosphorus pentachloride (5 g.), and phosphoryl chloride (50 c.c.) were heated under reflux for 3 hours at 130°. The excess of phosphoryl chloride was removed at 100° under reduced pressure, and the residual syrup dissolved in ice-water, treated with charcoal, filtered, and made alkaline with 10N-sodium hydroxide. The deposited whitish-grey solid was collected, drained, washed with water, and dried (5 g., m. p. 145—146°). Recrystallisation from water yielded white felted needles, m. p. 146—147°, of 4-chloro-*p*-phenanthroline (Kermack and Weatherhead, m. p. 146—147°).

Ethyl β-(8′-Chloro-6′-quinolylamino)-α-carbethoxyacrylate.—8-Chloro-6-aminoquinoline (5 g.) and ethyl ethoxymethylenemalonate (10 c.c.) were heated under reduced pressure at 100° on the water-bath for one hour to give a brownish solid (9·2 g., m. p. 136—140°) which was collected, drained, and washed with a small quantity of light petroleum (b. p. 60—80°); this recrystallised from ethanol in yellow-orange needles, m. p. 141—142°, of *ethyl β-(8′-chloro-6′-quinolylamino)-α-carbethoxyacrylate* (Found: C, 58·2; H, 4·9; N, 8·1. $C_{17}H_{17}O_4N_2Cl$ requires C, 58·5; H, 4·9; N, 8·0%).

*9-Chloro-4-hydroxy-3-carbethoxy-*p*-phenanthroline.*—The foregoing ester (9·2 g., m. p. 136—140°) was added in small portions with efficient stirring during 10 minutes to mineral oil (150 c.c.) at 250°, and the temperature maintained for a further 5 minutes. The cooled oil was filtered and the collected yellow-brown solid was well-drained, washed with light petroleum (b. p. 60—80°) till free from oil, and dried (7·5 g., m. p. 290—295° with frothing); recrystallisation from ethanol afforded cream needles (m. p. 311—312°, decomp.) of *9-chloro-4-hydroxy-3-carbethoxy-*p*-phenanthroline* (Found: C, 59·5; H, 3·7; N, 9·6. $C_{15}H_{11}O_3N_2Cl$ requires C, 59·5; H, 3·6; N, 9·3%).

*9-Chloro-4-hydroxy-3-carboxy-*p*-phenanthroline.*—The carbethoxy-compound (7·5 g.; m. p. 290—295°, decomp.) was heated under reflux on a water-bath with 20% methanolic potassium hydroxide (100 c.c.) for 6 hours. After 5 hours, gelatinous solid separated and was redissolved by addition of water (30 c.c.). The solution was treated with charcoal in an open flask for 5 minutes, filtered, and by the

addition of glacial acetic acid the pH was adjusted to 4. After standing for 12 hours, the solid was collected, drained, washed with water, and dried (6·5 g., m. p. 310—315° with frothing). Purification was achieved by dissolution in 2N-ammonium hydroxide and reprecipitation with 2N-acetic acid to give a light brown solid, m. p. 315—316° with frothing, or by recrystallisation from glacial acetic acid to give white fibrous needles, m. p. 319—320° with frothing, of 9-*chloro*-4-*hydroxy*-3-*carboxy*-p-*phenanthroline* (Found: C, 53·3; H, 3·2; N, 9·4. $C_{13}H_7O_3N_2Cl,H_2O$ requires C, 53·3; H, 3·1; N, 9·6%).

9-*Chloro*-4-*hydroxy*-p-*phenanthroline*.—The above acid (6·5 g., m. p. 310—315° with frothing) and copper–barium chromite catalyst (0·05 g.) were heated under reflux in dry, redistilled quinoline (130 c.c.) for 40 minutes. The solution was cooled to 100—140°, filtered, and, when cooled to room temperature, diluted with dry ether (500 c.c.) to deposit a brown solid, which was collected after 15 minutes, drained, washed liberally with fresh ether, and dried (4·5 g., m. p. 325°). This product, finely ground, was suspended in 2N-sodium carbonate for a few minutes, collected, drained, washed with cold water, and extracted 6 or 7 times with 100-c.c. portions of boiling water; the combined extracts were concentrated to 30—50 c.c., yielding yellow needles, after three purifications, m. p. 338—340°, of 9-*chloro*-4-*hydroxy*-p-*phenanthroline* (Found: C, 57·7; H, 3·5; N, 11·1. $C_{12}H_7ON_2Cl,H_2O$ requires C, 57·9; H, 3·6; N, 11·3%).

4 : 9-*Dichloro*-p-*phenanthroline*.—The foregoing chloro-compound (4 g., m. p. 325°), phosphorus pentachloride (4 g.), and phosphoryl chloride (40 c.c.) were heated under reflux for 4 hours at 140°. The excess of phosphoryl chloride was removed at 100° under reduced pressure, and the residual brownish syrup dissolved in ice-water to give a dark solution which was heated with charcoal, filtered, and made alkaline with 2N-sodium carbonate, depositing a greyish syrup which solidified after a few minutes. The solid was collected, washed with water, and dried (4 g., m. p. 225—226°). This 4 : 9-*dichloro*-p-*phenanthroline* recrystallised from ethanol in cream needles, m. p. 237—238° (Found: C, 57·6; H, 2·8; N, 11·1. $C_{12}H_6N_2Cl_2$ requires C, 57·8; H, 2·4; N, 11·25%).

NN′-*Bis*-(2 : 2-*dicarbethoxyvinyl*)-p-*phenylenediamine* (VI).—*p*-Phenylenediamine (5 g.) and ethyl ethoxymethylenemalonate (23 c.c.) were heated under reduced pressure at 100° on the water-bath for 30 minutes to yield a yellow solid, which was collected, drained, washed with light petroleum (b. p. 60—80°), and dried (17 g., m. p. 160—164°). Recrystallisation from ethanol (charcoal) yielded light yellow fibrous needles, m. p. 164—165°, of the *ester* (VI) (Found: C, 59·0; H, 6·3; N, 6·3. $C_{22}H_{28}O_8N_2$ requires C, 58·9; H, 6·25; N, 6·25%).

4 : 5-*Dihydroxy*-3 : 6-*dicarbethoxy*-p-*phenanthroline*.—(A) The preceding ester (17 g., m. p. 160—164°) was added in small amounts during 10 minutes to refluxing diphenyl (170 g.), and refluxing continued for a further 40 minutes. The mixture, cooled to 60—70°, was diluted with light petroleum (b. p. 80—100°) preheated to 70—80°, and filtered. The collected solid was extracted for 5 hours with boiling light petroleum (b. p. 80—100°) and dried (12 g., m. p. 255—260°).

(B) *p*-Phenylenediamine (5 g.) and ethyl ethoxymethylenemalonate (23 c.c.) were added to diphenyl (170 g.) and heated under reflux for 45 minutes. The product was isolated as in (A) (13·2 g., m. p. 255—260°). Recrystallisation from ethanol or aqueous pyridine yielded short white needles, m. p. 278—280° (after further drying, 283—284°), of 4 : 5-*dihydroxy*-3 : 6-*dicarbethoxy*-p-*phenanthroline* (Found: C, 57·8; H, 4·8; N, 7·95. $C_{18}H_{16}O_8N_2,H_2O$ requires C, 57·75; H, 4·8; N, 7·5%).

4 : 5-*Dihydroxy*-3 : 6-*dicarboxy*-p-*phenanthroline*.—The foregoing ester (10 g., m. p. 255—260°) was heated under reflux with 20% methanolic potassium hydroxide (100 c.c.) on a water-bath for 4 hours. Water (200 c.c.) was added, the solution treated with charcoal and filtered, and the pH adjusted to 5 with glacial acetic acid. The deposited solid was collected after 2 hours, drained, washed with water, and dried at 90° (6 g., m. p. 294—295° with frothing). This product was dissolved in 2N-ammonium hydroxide, treated with charcoal, filtered, and reprecipitated with 2N-acetic acid to yield, after three treatments, brown micro-needles, m. p. 297—298° with frothing, of 4 : 5-*dihydroxy*-3 : 6-*dicarboxy*-p-*phenanthroline* (Found: C, 50·1; H, 3·3; N, 8·4. $C_{14}H_8O_6N_2,2H_2O$ requires C, 50·0; H, 3·6; N, 8·3%).

4 : 5-*Dihydroxy*-p-*phenanthroline*.—(A) The dicarboxy-compound (10·3 g., m. p. 294—295°), copper–barium chromite catalyst (0·1 g.), and dry, redistilled quinoline (200 c.c.), preheated to 150°, were refluxed for one hour, cooled to 100°, filtered, and the filtrate concentrated (50 c.c.) under reduced pressure. The cold mixture was diluted with dry ether (500 c.c.), and the deposited solid collected, drained, washed thoroughly with ether, and dried (6·8 g., m. p. 345—350° with frothing). This compound could not be satisfactorily recrystallised from any of the common organic solvents but a relatively pure sample was obtained by extracting with a large volume of boiling water and concentrating (50 c.c.) the extract to yield yellow needles, m. p. 365—370° (decomp.), of 4 : 5-*dihydroxy*-p-*phenanthroline* (Found: C, 66·0; H, 3·9; N, 12·0. $C_{12}H_8O_2N_2,\frac{1}{2}H_2O$ requires C, 66·5; H, 3·9; N, 12·9%).

(B) 4 : 5-Dihydroxy-3 : 6-dicarboxy-*p*-phenanthroline (1 g., m. p. 294—295°) was heated at 300° in a dry test-tube till frothing ceased to yield a black residue which was treated with 2N-ammonium hydroxide, washed with water, and dried (0·6 g., m. p. 340—350°); this recrystallised from a large volume of boiling water to yield 4 : 5-dihydroxy-*p*-phenanthroline, m. p. 365—370° (decomp.).

4 : 5-*Dichloro*-p-*phenanthroline*.—4 : 5-Dihydroxy-*p*-phenanthroline (6·5 g., m. p. 350°), phosphorus pentachloride (13 g.), and phosphoryl chloride (130 c.c.) were heated under reflux for 7 hours at 140°. Excess of phosphoryl chloride was removed under reduced pressure on a water-bath, and the residual syrup was dissolved in ice-water, treated with charcoal, and rendered alkaline with 10N-sodium hydroxide. Yellow needles were deposited; these were collected, drained, washed with water, and dried (4·3 g., m. p. 235—240°). Recrystallisation from ethanol yielded yellow needles, m. p. 247—248°, of 4 : 5-*dichloro*-p-*phenanthroline* (Found: C, 57·8; H, 2·7; N, 11·3. $C_{12}H_6N_2Cl_2$ requires C, 57·8; H, 2·4; N, 11·3%).

9-*Chloro*-4-(3′-*diethylaminopropylamino*)-p-*phenanthroline*.—4 : 9-Dichloro-*p*-phenanthroline (3·1 g., m. p. 237—238°) and 3-diethylaminopropylamine (6·2 c.c.) were heated under reflux for 6 hours at 160—170°. The excess of amine was removed under reduced pressure, and the residual syrup dissolved in 2N-hydrochloric acid, the solution filtered, made alkaline with 2N-ammonium hydroxide, and

extracted with ether, the extract dried (K_2CO_3) for 6 hours, the solvent removed, and the residual brown oil dissolved in the minimum quantity of ethanol, to which a saturated ethanolic solution of 3 : 5-dinitrobenzoic acid was added till no further precipitate formed. The deposited yellow solid (9 g.) was collected and recrystallised from ethanol three times to yield yellow needles, m. p. 193—194°, of the *bis*-3 : 5-*dinitrobenzoate* of 9-chloro-4-(3′-diethylaminopropylamino)-*p*-phenanthroline (Found: C, 51·75; H, 4·0; N, 14·3. $C_{18}H_{23}N_4Cl,2C_7H_4O_6N_2$ requires C, 51·7; H, 4·1; N, 14·6%).

4-(4′-*Diethylamino*-1′-*methylbutylamino*)-p-*phenanthroline*.—4-Chloro-*p*-phenanthroline (1·4 g., m. p. 145—146°), redistilled 2-amino-5-diethylaminopentane (3 c.c.), a trace of copper powder, and a small crystal of iodine were heated under reflux for 5 hours at 180°. The product was worked up as described for the previous compound, and converted into a 3 : 5-dinitrobenzoate (5 g., m. p. 120—125°) which on recrystallisation three times from ethanol yielded yellow needles, m. p. 160—161° (loses solvent about 125°), of the *tris*-3 : 5-*dinitrobenzoate* of 4-(4′-diethylamino-1′-methylbutylamino)-*p*-phenanthroline (Found: C, 52·3; H, 4·3; N, 13·8. $C_{21}H_{28}N_4,3C_7H_4O_6N_2,C_2H_5{\cdot}OH$ requires C, 51·9; H, 4·5; N, 13·75%).

4 : 5-(3′-*Diethylaminopropylimino*)-p-*phenanthroline*.—4 : 5-Dichloro-*p*-phenanthroline (1·2 g., m. p. 247—248°) and 3-diethylaminopropylamine (6 c.c.) were heated under reflux at 160° for 18 hours. The excess of amine was removed under reduced pressure, and the residual product was dissolved in 2N-acetic acid, filtered, extracted with ether till no further yellow colour was obtained in the ether, rendered alkaline with 2N-ammonium hydroxide, and again extracted with ether; the extract was dried (K_2CO_3) and the solvent removed to yield, after two treatments, a brown oil (2 g.) which was, after unsuccessful attempts to prepare other salts which proved deliquescent, dissolved in ethanol and treated with a saturated ethanolic solution of 3 : 5-dinitrobenzoic acid. The supernatant liquid was decanted, and the syrup dissolved in methanol and allowed to crystallise; three further recrystallisations from methanol yielded soft cream needles, m. p. 194—195°, of the *bis*-3 : 5-*dinitrobenzoate* of 4 : 5-(3′-*diethylaminopropylimino*)-p-*phenanthroline* (Found: C, 53·9; H, 4·1; N, 15·4. $C_{19}H_{22}N_4,2C_7H_4O_6N_2$ requires C, 54·25; H, 4·1; N, 15·3%).

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217. *Production of Antibiotics by Fungi. Part IV. Lateritiin-I, Lateritiin-II, Avenacein, Sambucinin, and Fructigenin.*

By A. H. COOK, S. F. COX, and T. H. FARMER.

The isolation and degradation of *lateritiin-I, lateritiin-II, avenacein, sambucinin, and fructigenin* are described.

IT was observed (Cook, Cox, Farmer, and Lacey, *Nature*, 1947, **160**, 31) that metabolism solutions obtained from *F. lateritium* (two strains), *F. avenaceum*, *F. sambucinum*, and *F. fructogenum* inhibited the growth of *Mycobacterium phlei* at a limiting dilution of 1 : 20 but were only weakly active against *Staphylococcus aureus*. These fungi were studied more closely in view of the possibility of the active principles inhibiting the pathogen, *M. tuberculosis*. The results now communicated were presented at the XIth International Congress of Pure and Applied Chemistry held in London in July, 1947.

The antibiotics were produced by the fungi in the presence of a nitrogen source (" Bactotryptone " or " Eupepton "), glucose, and inorganic salts, and could be extracted with organic solvents such as light petroleum or ether. Preliminary experiments showed the active principles to be insensitive to heat and acid, but sensitive to alkali. Crude material from an ether extract of the medium (pH = 5·5) was purified by chromatography, although, in general, light petroleum extracts afforded material which, after treatment with charcoal, could be purified by crystallisation from aqueous methanol. In this manner the pure antibiotics *lateritiin-I*, m. p. 121—122°, *lateritiin-II*, m. p. 125°, *avenacein*, m. p. 139°, *sambucinin*, m. p. 86—87°, and *fructigenin*, m. p. 129°, were isolated; the m. p. of each antibiotic was depressed on admixture with any one of the others. *Sambucinin* was chromatographed on neutral alumina in order to determine whether it was a mixture of compounds but no further purification was effected.

All five antibiotics contained only carbon, hydrogen, oxygen, and nitrogen, and were neutral compounds. Analyses and molecular-weight determinations on samples from several batches indicated the following formulæ for the antibiotics: lateritiin-I, $C_{26}H_{46}O_7N_2$; lateritiin-II, $C_{26}H_{46}O_7N_2$; avenacein, $C_{25}H_{44}O_7N_2$; sambucinin, $C_{24}H_{42}O_7N_2$; fructigenin, $C_{26}H_{44-46}O_7N_2$. The five compounds contained neither active hydrogen atoms nor methoxyl groups; lateritiin-I, avenacein, and fructigenin contained two *N*-methyl groups and at least four *C*-methyl groups.

They showed ultra-violet absorption only below $\lambda = 219$ mμ. The stability of the compounds to heat and acid was exemplified by lateritiin-I which only lost 10% of its activity on distillation in a tube over an open flame, and 50% of its activity on heating with concentrated nitric acid at 100° for 1 hour. Although dilute caustic alkali caused rapid inactivation at room temperature, greater stability was exhibited towards ammonia, morpholine, and other bases. Complete saturation was demonstrated by means of neutral permanganate, bromine in chloroform, and unsuccessful catalytic hydrogenation.

Vigorous acid hydrolysis of lateritiin-I yielded a solution which on ether extraction afforded a colourless acid, m. p. 65—66°, in the form of plates. Water solubility, a yellow colouration with dilute ferric chloride solution, and sensitivity to oxidising agents suggested the presence of an α-hydroxy-acid, since a β-hydroxy-acid would have formed a halogeno-paraffin under the conditions of hydrolysis (Perkin, *J.*, 1896, **69**, 1484) and a γ- or δ-hydroxy-acid would have lactonised. Microelectrometric titrations, molecular-weight determinations, and analyses of the acid and its benzylamine salt indicated a formula, $C_5H_{10}O_3$. The acid was optically active, $[\alpha]_D$ −19·4° ±2·6° (c = 0·95% in chloroform) and, on oxidation with lead tetra-acetate, a reaction which verified the location of the hydroxyl group on the α-carbon atom, yielded an aldehyde which was volatile in steam and characterised as its 2 : 4-dinitrophenylhydrazone, *p*-nitrophenylhydrazone, and 2 : 4-dinitrophenylsemicarbazone. Analysis, and mixed m. p.s of each of the three derivatives with authentic *iso*butaldehyde derivatives identified the acid as one of the optical isomers of α-hydroxy*iso*valeric acid :

$$CHMe_2{\cdot}CH(OH){\cdot}CO_2H \xrightarrow{Pb(OAc)_4} CHMe_2{\cdot}CHO.$$

Although both forms of α-hydroxy*iso*valeric acid had been previously prepared (Fischer and Scheibler, *Ber.*, 1908, **31**, 2897; Bartlett, Kunz, and Levene, *J. Biol. Chem.*, 1937, **118**, 508) no m. p.s had been recorded; therefore specimens of the two enantiomorphs were obtained by deaminating D- and L-valine with nitrous acid (Fischer and Scheibler, *loc. cit.*). It has been demonstrated that in this reaction no inversion occurs and a hydroxy-acid, with the same configuration as the amino-acid, is obtained (Clough, *J.*, 1918, **113**, 526; Freudenberg and Rhino, *Ber.*, 1942, **57**, 1547). The results summarised in the table below show that D-α-hydroxy*iso*valeric acid is identical with the degradation acid.

	$[\alpha]_D$ ($CHCl_3$).	$[\alpha]_D$ (N-NaOH).	$[\alpha]_D$ (H_2O).	M. p.	Mixed m. p.
D-α-Hydroxy*iso*valeric acid	−19·9° ± 1·8°	+10·8° ± 2·0°	−3·2° ± 1·8°	64·5°	65·0°
L-α-Hydroxy*iso*valeric acid...	+16·9° ± 2·0°	−11·1° ± 2·0°	+2·9° ± 2·0°	65°	81—82°
Acid under investigation.....	−19·4° ± 2·6°	+12·7° ± 1·8°	−2·3° ± 2·0°	65—66°	—

The yields of D-α-hydroxy*iso*valeric acid from the hydrolysis approximated to 2 mols. per mol. of lateritiin-I.

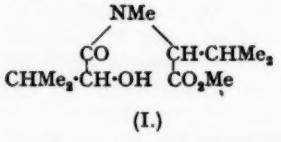
Evaporation of the acid hydrolysate, after ether extraction, gave a colourless gum which showed a tendency to crystallise on vigorous drying. Careful precipitation with ether from an ethanol solution afforded colourless needles, m. p. 149°, $[\alpha]_D^{15°}$ +25·5° ±1·1° (c = 1·75% in ethanol), of a base hydrochloride. Electrometric titrations and analyses indicated a molecular formula $C_6H_{13}O_2N$,HCl, and the presence of a weak acidic grouping. The failure to obtain a positive ninhydrin reaction or effervescence with nitrous acid with the free base, m. p. 265°, were in accordance with further analyses which showed the presence of one *N*-alkyl group. The evidence suggested a methylamino-acid, and samples of the crude and purified base were treated with sodium hypobromite and the products decomposed with steam (Langheld, *Ber.*, 1909, **42**, 2366). In both cases only one carbonyl compound was formed, as demonstrated by the chromatography of its 2 : 4-dinitrophenylhydrazone, and it was identified as *iso*butaldehyde (2 : 4-dinitrophenylhydrazone, m. p. 168°; 2 : 4-dinitrophenylsemicarbazone, m. p. 204°; *p*-nitrophenylhydrazone, m. p. 130°). From the degradation, methylamine was also isolated as its hydrochloride, m. p. 217° (mixed m. p. 219°). The final proof of the homogeneity of the methylamino-acid was obtained by chromatographing a specimen of the crude material on a strip of paper and development with aqueous methanolic cupric acetate; one band only was found. The isolation of *iso*butaldehyde proved that the methylamino-acid was one of the optically active forms of *N*-methylvaline, and on comparison with other methylamino-acids it appeared that the acid probably had an L-configuration. A sample of *N*-methyl-L-valine was prepared from L-valine (Fischer and Lifschitz, *Ber.*, 1915, **48**, 363), and the hydrochloride found not to give a depression of m. p. with the base hydrochloride under discussion. It was also obtained by treatment of L-α-bromo*iso*valeric acid with aqueous methylamine solution and was

again identical with the material of natural origin. Yields of *N*-methyl-L-valine from hydrolyses approximated to 2 mols. per mol. of antibiotic. Lateritiin-I, lateritiin-II, avenacein, fructigenin, and sambucinin formed D-α-hydroxy*iso*valeric acid and *N*-methyl-L-valine on acid hydrolysis in similar yields. In these hydrolyses small amounts of *iso*butaldehyde were detected but these were demonstrated to be formed by D-α-hydroxy*iso*valeric acid alone, under identical conditions.

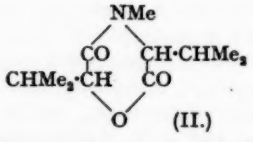
The rapid inactivation of lateritiin-I with dilute sodium hydroxide at room temperature afforded another method of degradation. Electrometric titrations on solutions of lateritiin-I which had been allowed to stand with this reagent for increasing periods of time, indicated the formation of an acidic grouping, the amount of which was proportional to the decrease in activity. The final titration corresponding to total inactivation gave an equivalent of 247, and the simple nature of the curve indicated that two molecules of the acid were formed from one of the antibiotic. Initial experiments resulted in the isolation of a gummy acid which could not be crystallised and failed to give crystalline derivatives. It was observed that this material lost its acidic properties, on standing at room temperature for 3 days, to give a colourless, neutral oil, a change which was accelerated by distillation in a high vacuum. By following the alkali inactivation polarimetrically it was found that, whereas lateritiin-I, the sodium salt of the degradation acid, and the free acid had comparable specific rotations, that of the last gradually changed from $-93°$ to $+167°$ at pH 1·5, demonstrating the occurrence of a chemical change. This change was shown to be a ring closure with loss of water and not a decarboxylation. In two hours the acid was converted quantitatively into the neutral product at 100°. Analysis of the *product*, indicated a formula $C_{11}H_{19}O_3N$, and on acid hydrolysis D-α-hydroxy*iso*valeric acid and *N*-methyl-L-valine were obtained. By reaction of a sample of the free acid with diazomethane a crystalline *methyl* ester, $C_{12}H_{23}O_4N$, was prepared and characterised as the *α-naphthylamine* adduct of the 3 : 5-dinitrobenzoyl derivative. Alkaline hydrolysis of sambucinin and fructigenin gave an acid of which the methyl ester was identical with the corresponding compound from lateritiin-I.

The same ester was obtained by hydrolysis of the lactone with dilute alkali followed by treatment with diazomethane, and must on the above evidence be regarded as the methyl ester of D-α-hydroxy*iso*valeryl-*N*-methyl-L-valine (I), while the lactone is 2 : 5-diketo-4-methyl-3 : 6-di*iso*propylmorpholine (II). These structures were verified by comparison with synthetic materials, obtained by condensing L-α-bromo*iso*valeric acid chloride with *N*-methyl-DL-valine and replacement of the bromine in the product with a hydroxyl group by boiling with pyridine and water. The acid formed lost water spontaneously when kept, and on separation of the two disastereoisomers of the lactone by chromatography on acid alumina, a product was obtained identical in all respects with the natural material. This yielded a crystalline methyl ester, m. p. 75°, on hydrolysis and reaction with diazomethane, which had the same physical properties as the natural ester and gave no depression of melting point on admixture.

The differences in the structures of lateritiin-I, lateritiin-II, avenacein, sambucinin, and fructigenin are attributed to the presence of small fragments in the antibiotic molecules which are yet unidentified. Selective *in situ* oxidation experiments (Williams and Woods, *J. Amer. Chem. Soc.*, 1937, **57**, 1408) on acid hydrolysates failed to show the presence of this fragment, as did attempts to isolate a volatile product from alkaline inactivations. In the latter instance the titration curves obtained in earlier studies exclude the possibility of an acidic or basic fragment.



(I.)



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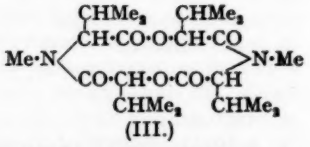

(III.)

Since the announcement of these results in 1947, Plattner and Nager (*Helv. Chim. Acta*, 1948, **31**, 665) have described the degradation of the antibiotic enniatin B, $C_{33}H_{38}O_6N_3$, m. p. 175—175·5°. Acid hydrolysis of this compound afforded two molecules each of D-α-hydroxy*iso*valeric acid and *N*-methyl-(+)-valine; a compound formulated as D-α-hydroxy*iso*valeryl-*N*-methyl-(+)-valine methyl ester was obtained on esterifying the acid obtained by degradation with alkali. No other degradation products were found and the antibiotic was given the structure (III).

The m. p. of enniatin A, $C_{34}H_{62}O_6N_3$, was not depressed on admixture with lateritiin-I and the two compounds might appear to be identical from *X*-ray examination. Enniatin A, however, afforded *N*-methyl-(+)-leucine on degradation, and Plattner and Nager suggest that the valine

derivative obtained from lateritiin-I arises as a gross impurity. In view of the data reported in the present paper this suggestion cannot be accepted, for, in addition, the crude degradation product was submitted to paper chromatography and showed no sign of heterogeneity. Moreover, the structure proposed by the Swiss workers must be viewed with reserve; the antibiotics described in the present paper give rise to degradation products which so far have been unvarying, and as enniatins A and B, lateritiins-I and -II, avenacein, sambucinin, and fructigenin are obviously similarly constituted, acceptance of formula (III) would imply one structure to represent several demonstrably different antibiotics.

Experimental.

The fungi were grown on a medium prepared by dissolving Eupepton No. 2 (100 g.), glucose (100 g.), and sodium chloride (50 g.) in tap water (10 l.), and distributed in quart-size milk bottles (each containing 400 c.c.). Before inoculation the medium was sterilised at 15 lbs. pressure of steam for 15 minutes, and the plugged bottles placed in an almost horizontal position in the incubating room. After inoculation the fungi were allowed to grow for 13—14 days at 25°, by which time the medium had reached maximum antibacterial titre.

Extraction of Lateritiin-I.—The active medium (18 l.) was extracted three times with light petroleum (3 × 1·5 l.), and the extract dried (Na_2SO_4). On evaporation, an almost colourless gum was obtained which was dissolved in methanol (20 c.c.), filtered, and the solution heated to boiling with norite (200 mg.). The filtrate (15 c.c.) was diluted with water (85 c.c.) and allowed to stand for 15 hours. Colourless plates were deposited (754 mg.), m. p. 110—112°. Repeated crystallisation from aqueous methanol gave *lateritiin*-I, m. p. 121—122°, $[\alpha]_D^{20°}$ −95·6° ± 2·0° (*c* = 1% in ethanol) (Found, on different samples: C, 62·77, 62·92, 62·13, 62·41, 62·77, 62·66, 62·90, 62·57; H, 9·23, 9·08, 9·24, 9·00, 8·98, 9·24, 9·02, 9·12; N, 5·92, 6·12, 5·99, 6·05, 6·03, 6·30; *C*-Me, 13·9; *N*-Me, 5·7; *M*, cryoscopic in camphor, 523. $C_{26}H_{46}O_7N_2$ requires C, 62·66; H, 9·24; N, 5·62; 5*C*-Me, 15·1; 2*N*-Me, 6·0%; *M*, 498).

The culture fluids of *F. avenaceum*, *F. sambucinum*, *F. fructigenum*, and *F. lateritium*-II were extracted in a similar manner to those of *F. lateritiin*-I, and the products recrystallised from aqueous methanol. *Avenacein* was obtained in colourless tetrahedra, m. p. 139°, $[\alpha]_D^{19°}$ −101° ±2·0° (*c* = 1% in ethanol) (Found, on different samples: C, 62·08, 61·98, 62·03, 61·77, 61·98, 61·87, 61·84, 62·00; H, 8·93, 8·91, 8·92, 8·80, 8·87, 8·89, 8·81, 8·91; N, 6·03, 5·85, 6·17, 5·83, 5·83; *C*-Me, 14·6; *N*-Me, 5·8; *M*, cryoscopic in camphor, 489, 492, 494. $C_{25}H_{44}O_7N_2$ requires C, 61·98; H, 9·09; N, 5·78; 5*C*-Me, 15·5; 2*N*-Me, 6·2%; *M*, 484).

Lateritiin-II crystallised in colourless plates, m. p. 125°, $[\alpha]_D^{19°}$ −92·0° ±1·6° (*c* = 1·2% in ethanol) (Found, on different samples: C, 62·37, 62·70, 62·40, 62·06, 62·28, 62·47, 62·57; H, 9·07, 9·13, 9·15, 9·08, 8·97, 8·98, 9·22; N, 6·10, 6·09, 6·07. $C_{26}H_{46}O_7N_2$ requires C, 62·66; H, 9·2; N, 5·62%).

Sambucinin was originally obtained as a crude product, m. p. 71—78°. A sample was crystallised five times from aqueous methanol to afford colourless plates, m. p. 86—87°, $[\alpha]_D^{21°}$ −83·2° ±2·0° (*c* = 1% in ethanol) (Found, on different samples: C, 61·18, 61·20, 60·95, 61·18; H, 9·15, 9·29, 9·40, 9·20; N, 5·81. $C_{24}H_{42}O_7N_2$ requires C, 61·20; H, 8·93; N, 5·96%).

Fructigenin crystallised in colourless plates, m. p. 129°, $[\alpha]_D^{18°}$ −103° ±2° (*c* = 1% in ethanol) (Found, on different samples: C, 63·13, 62·92, 62·96, 63·15; H, 8·80, 8·73, 8·89, 8·73; N, 5·78, 5·49, 5·55, 5·63; *C*-Me, 12·6; *N*-Me 5·6. $C_{26}H_{46}O_7N_2$ requires C, 62·66; H, 9·24; N, 5·26; 4*C*-Me, 12·1; 2*N*-Me, 6·0. $C_{26}H_{44}O_7N_2$ requires C, 62·95, H, 8·88; N, 5·65; 4*C*-Me, 12·1; 2*N*-Me, 6·0%).

Extraction of Lateritiin-I from the Mycelium of F. lateritium-I.—The mycelium from 20 l. of medium was well washed with water, dried by suction, and heated at 50° for 48 hours. A brittle mass (135 g.) was obtained which was ground to a powder and extracted with light petroleum to yield a pale amber solution which on evaporation afforded a brown oily gum. The gum was extracted with boiling methanol (20 c.c.), and the solution decolourised with norite (0·4 g.) and diluted with water (80 c.c.). Colourless irregular plates (102 mg.) were formed, m. p. 112°. On recrystallising three times from aqueous methanol lateritiin-I, m. p. 121°, was obtained. Many other samples of dried mycelium yielded no antibiotic and the mycelium was usually not treated as a source of lateritiin-I.

Extraction of Fructigenin from the Mycelium of F. fructigenum.—The mycelium from 30 l. of culture fluid was pressed mechanically to remove most of the water and pulped with hot acetone (4 × 500 c.c.). On evaporation in a vacuum, a pasty mass was obtained which was extracted with chloroform, and the extract was chromatographed on neutral alumina. 1 G. of a biologically active fraction, m. p. 89°, was obtained which on repeated recrystallisation from methanol–water yielded fructigenin, m. p. 128—129° (0·5 g.). On another occasion the yield of antibiotic was much smaller.

Vigorous Acid Hydrolysis of Lateritiin-1.—(A) *Isolation and identification of* D-α-*hydroxyisovaleric acid.* Lateritiin-I (675 mg.) was sealed in a glass tube with hydrochloric acid (5 c.c.) and heated to 125° in an oil-bath for 5 hours. After cooling, the contents of the tube were diluted with water (8 c.c.) and extracted three times with ether (3 × 10 c.c.). The ethereal extract was dried and evaporated to give a pale brown gum (370 mg.) which crystallised on scratching. Recrystallisation from benzene–light petroleum gave colourless plates which when pure had m. p. 65—66°, $[\alpha]_D^{15°}$ −21·2° ±1·6° (*c* = 1·25% in chloroform) (Found: C, 51·0; H, 8·6. Calc. for $C_5H_{10}O_3$: C, 50·85; H, 8·5%). The *benzylamine* salt melted at 134° (Found: C, 64·1; H, 8·3; N, 6·4. $C_5H_{10}O_3,C_7H_9N$ requires C, 64·0; H, 8·4; N, 6·2%).

Oxidation of D-α-*hydroxyisovaleric acid with lead tetra-acetate* (cf. Oeda, *Bull. Chem. Soc. Japan*, 1934, **9**, 8). D-α-Hydroxy*iso*valeric acid (37 mg.) was dissolved in A.R. glacial acetic acid (3 c.c.) containing lead tetra-acetate (139 mg.), and the mixture kept at 50—60° under reflux for 1½ hours. The reaction solution was cooled, diluted with ice water (5 c.c.), and adjusted to pH 7·5 with solid sodium hydrogen carbonate. On steam-distillation a distillate was obtained which gave a precipitate with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. Chromatography of the precipitate yielded deep yellow laths, m. p. 168°, of the dinitrophenylhydrazone (Found: C, 47·5; H, 4·8. Calc. for $C_{10}H_{18}O_4N_4$:

C, 47·6; H, 4·8%). A further oxidation yielded an aqueous distillate from which a *p*-nitrophenylhydrazone, m. p. 130°, and a 2 : 4-dinitrophenylsemicarbazone, m. p. 204°, were prepared. Admixture with the corresponding *iso*butaldehyde derivatives led to no depression of m. p.

Preparation of D-α-*hydroxyisovaleric acid* (Fischer and Scheibler, *Ber.*, 1908, **31**, 2897). D-Valine (1 g.) was dissolved in 2N-sulphuric (16 c.c.) and treated with a solution of sodium nitrite (0·9 g.) to give D-α-hydroxy*iso*valeric acid (545 mg.), m. p. 65—66°, $[\alpha]_D^{14°}$ −19·9° ±1·8° (*c* = 1% in chloroform).

L-α-Hydroxy*iso*valeric acid (470 mg.) was similarly prepared from L-valine (1 g.), and obtained in colourless plates, m. p. 65°, $[\alpha]_D^{14°}$ +16·9° ± 2·0° (*c* = 1% in chloroform).

(B) *Isolation and identification of* N-*methyl*-L-*valine.* The acid solution from the acid hydrolysis of lateritiin-I (675 mg.), after ether extraction, was evaporated to dryness to give a colourless gum (524 mg.) which on intensive drying crystallised slowly. By dissolving the gum in dry ethanol, diluting with sodium-dried ether, and " seeding ", colourless needles were obtained, together with some gum. The latter was recrystallised in the same manner to give a total yield of 372 mg. Fractional crystallisation of the impure *hydrochloride* revealed the presence of only one distinct compound, m. p. 149°, $[\alpha]_D^{18°}$ +25·5° ±1·1° (*c* = 1·75% in ethanol) (Found: C, 43·3; H, 8·1; N, 8·5; *N*-Me, 16·9. $C_6H_{13}O_2N$,HCl requires C, 43·0; H, 8·4; N, 8·4; *N*-Me, 17·3%).

The free N-*methyl*-L-*valine* was obtained by two methods. (1) The powdered hydrochloride (100 mg.) was treated with a slight excess of ethereal diazomethane for 2 minutes and the excess of diazomethane rapidly taken off under reduced pressure; the powdery white solid (78 mg.) which remained was crystallised from aqueous acetone and yielded colourless plates which sublimed at 250—260° and melted at 265° (Found: C, 55·0; H, 9·75. $C_6H_{13}O_2N$ requires C, 54·95; H, 9·9%).

(2) The gummy hydrochloride (110 mg.) was dissolved in water and shaken with silver sulphate (140 mg.) for 1 hour. The solution was filtered, made just alkaline with dilute baryta, and refiltered. The filtrate was adjusted to pH 7 with dilute sulphuric acid, and, after centrifuging, the supernatant liquid was evaporated to dryness. Crystallisation of the residue from aqueous acetone gave colourless plates (62 mg.), m. p. 265°.

Paper-chromatography of the Crude Methylamino-acid.—A sample of the crude methylamino-acid (30 μg.) was chromatographed at 25° on a strip of Whatman No. 1 filter paper, 35 × 2 cm. After 18 hours the phenol had flowed 28 cm. down the paper strip, which was then removed and " dried " in a steam oven. By spraying the chromatogram with 75% aqueous methanolic copper acetate solution one band only was observed.

Oxidation of the Crude N-*Methyl*-L-*valine with Sodium Hypobromite* (cf. Langheld, *Ber.*, 1909, **42**, 2366).—Crude *N*-methyl-L-valine hydrochloride was dissolved in water (5 c.c.), and the solution adjusted to pH 7·5 with dilute sodium hydroxide. To this solution at 0° was added N-sodium hypobromite (2·1 c.c.), and the mixture allowed to stand for 30 minutes, then cooled to −10° and dropped into a current of steam during the course of 3 minutes. The distillate was collected in a cooled flask containing 2N-hydrochloric acid (5 c.c.). Distillation of the acid solution separated the aldehyde from the amine hydrochloride. The aqueous aldehyde was converted into its 2 : 4-dinitrophenylhydrazone (262 mg.) and *p*-nitrophenylhydrazone (90 mg.), which were separately chromatographed on alumina to give one crystalline derivative in each case. The 2 : 4-dinitrophenylhydrazone, m. p. 168°, formed deep yellow laths (Found: C, 47·8; H, 4·2. Calc. for $C_{10}H_{12}O_4N$: C, 47·6; H, 4·7%), and the *p*-nitrophenylhydrazone formed orange needles, m. p. 130°. These compounds when admixed with the corresponding *iso*butaldehyde derivatives showed no depression of m. p.

The amine hydrochloride (60·5 mg.) was obtained on evaporation of the acid solution, and crystallisation from dry ethanol–ether afforded colourless, hygroscopic needles, m. p. 217°. When admixed with methylamine hydrochloride (m. p. 220°) the mixture melted at 219°.

The pure methylamino-acid (51 mg.) was oxidised in a similar manner with 1N-sodium hypobromite (0·45 c.c.), and the 2 : 4-dinitrophenylsemicarbazone (16·1 mg.) of the aldehyde prepared. Crystallisation from ethanol–acetic acid yielded dull amber needles, m. p. 204°, which did not depress the m. p. of an authentic sample of *iso*butaldehyde 2 : 4-dinitrophenylsemicarbazone (Found: C, 45·1; H, 4·5. Calc. for $C_{11}H_{13}O_5N_5$: C, 44·75; H, 4·4%).

Preparation of N-*Methyl*-L-*valine from* L-*Valine* (cf. Fischer and Lifschitz, *Ber.*, 1915, **48**, 360).—L-Valine (1 g.) was dissolved in 2N-sodium hydroxide (4·7 c.c.) and treated with toluene-*p*-sulphonyl chloride (3·22 g.) in ether (8·5 c.c.). The *toluene*-p-*sulphonyl*-L-*valine* (1·339 g.) crystallised from water in colourless needles, m. p. 146—147°, $[\alpha]_D^{21°}$ +19·4° ±2·6° (*c* = 1·45% in ethanol) (Found: C, 53·1; H, 6·4. $C_{12}H_{17}O_4NS$ requires C, 53·1; H, 6·3%).

Tosyl-L-valine (1 g.) was dissolved in 2N-sodium hydroxide (6·35 c.c.) and methylated with methyl iodide (0·93 g.) under pressure to give a pale yellow gum (0·98 g.), $[\alpha]_D^{21°}$ −20·8° ±2·1° (*c* = 1·5% in ethanol). The toluene-*p*-sulphonyl-*N*-methyl-L-valine (324 mg.) was hydrolysed by sealing in a tube with fuming hydrochloric acid (*d* 1·19, 5 c.c.) and heating at 100° for 20 hours. The solution was evaporated to dryness and N-*methyl*-L-*valine hydrochloride* (15·1 mg.) was isolated; it had m. p. 146°, $[\alpha]_D^{19°}$ +18·9° ±2·4° (*c* = 0·85% in ethanol) (Found: C, 43·7; H, 7·9. $C_6H_{13}O_2N$,HCl requires C, 43·0; H, 8·3%). Admixture with the natural methylamino-acid hydrochloride raised the m. p. to 148°.

Preparation of N-*Methyl*-L-*valine from* L-α-*Bromoisovaleric Acid.*—L(−)-α-Bromo*iso*valeric acid (Levene, Mori, and Mikeska, *J. Biol. Chem.*, 1927, **65**, 348) (2 g.) was dissolved in ice-cold 33% methylamine solution (30 c.c.) and kept at 30° for 48 hours. N-Sodium hydroxide solution (25 c.c.) was added, and the solution evaporated to dryness in a vacuum. The gummy residue was dissolved in 2N-hydrochloric acid (15 c.c.), extracted with ether (2 × 25 c.c.), and the aqueous layer neutralised with sodium hydroxide. It was again evaporated to dryness, and the residue extracted repeatedly with ethanol (25 c.c.), whereupon *N*-methyl-L-valine (0·4 g.) was obtained. This was treated with aqueous hydrochloric acid, dried in a vacuum, and recrystallised four times from ethanol–ether. A product was obtained, m. p. 148°, $[\alpha]_D^{21°}$ +19·5° ±2° (*c* = 1·0% in ethanol), which gave no depression of m. p. on admixture with the natural amino-acid hydrochloride.

Vigorous Acid Hydrolysis of Avenacein.—Avenacein (200 mg.) was hydrolysed with hydrochloric acid (2 c.c.) in a sealed tube at 120° for 5 hours. Ether extraction of the hydrolysate yielded D-α-hydroxy-

*iso*valeric acid (79 mg.), m. p. 65—66°, $[\alpha]_D^{20°}$ −20·1° ±2° (*c* = 1% in chloroform); mixed m. p. with an authentic sample, 65°. The benzylamine salt, m. p. 134°, was also prepared. The remaining aqueous solution yielded a hydrochloride (121 mg.) which was identical with *N*-methyl-L-valine hydrochloride, m. p. 149°, $[\alpha]_D^{18°}$ +24·8° ±2·1° (*c* = 0·88% in ethanol). When mixed with an authentic sample the m. p. of the hydrochloride was not depressed.

Vigorous Acid Hydrolysis of Sambucinin.—Hydrolysis of sambucinin (203 mg.) with concentrated hydrochloric acid (2 c.c.) afforded D-α-hydroxy*iso*valeric acid (72 mg.), m. p. 65—66°, $[\alpha]_D^{18°}$ −19·5° ±1·8° (*c* = 1·15% in chloroform), and *N*-methyl-L-valine hydrochloride (124 mg.), m. p. 148—149°, $[\alpha]_D^{18°}$ +25·1° ±2·0° (*c* = 1% in ethanol).

Vigorous Acid Hydrolysis of Lateritiin-II.—Lateritiin-II (150 mg.) was hydrolysed with concentrated hydrochloric acid (1·5 c.c.) to give D-α-hydroxy*iso*valeric acid (54 mg.), m. p. 65°, $[\alpha]_D^{20°}$ −18·4° ±2·2° (*c* = 0·90% in chloroform), and *N*-methyl-L-valine hydrochloride (89 mg.), m. p. 149°, $[\alpha]_D^{21°}$ +25·3° ± 1·9° (*c* = 1·16% in ethanol).

Vigorous Acid Hydrolysis of Fructigenin.—Hydrolysis of fructigenin (300 mg.) with concentrated hydrochloric acid (4 c.c.) for 6 hours at 120—125° yielded D-α-hydroxy*iso*valeric acid (98 mg.), m. p. 65°, $[\alpha]_D^{19°}$ −19·1° ±2° (*c* = 1·0% in chloroform), and *N*-methyl-L-valine hydrochloride (160 mg.), m. p. 148°, $[\alpha]_D^{19°}$ +24·1° ±2° (*c* = 0·95% in ethanol).

D-α-Hydroxy*iso*valeric acid (1·470 mg.) was titrated electrometrically with 0·051N-sodium hydroxide: equiv., 129; pK_a' 3·6. Electrometric titration of *N*-methyl-L-valine hydrobromide (2·869 mg.) with 0·051N-sodium hydroxide showed equiv., 226; pK_a' 10·1.

(C) *Mild Alkaline Hydrolysis of Lateritiin-I.*—Lateritiin-I (435 mg.) was dissolved in methanol (5 c.c.) and kept with 2N-sodium hydroxide (2·5 c.c.) at room temperature for 16 hours. The reaction mixture was diluted with water (10 c.c.), extracted three times with ether (3 × 10 c.c.), and then acidified to pH 1·5 with 2N-sulphuric acid. The solution became turbid on acidification but cleared on ether extraction (4 × 10 c.c.). The extract was dried and evaporated at 30° to give a colourless acidic gum (425 mg.). On standing for 3 days at room temperature a portion of the gum lost its acidity. The remainder (355 mg.) was transferred to a small distillation tube and distilled at 75° in high vacuum to give a colourless, viscous, neutral oil (307 mg.) (Found: C, 62·1; H, 8·9; N, 6·5. $C_{11}H_{19}O_3N$ requires C, 62·0; H, 8·9; N, 6·6%).

Quantitative conversion of acid into lactone. A sample of gummy acid (559 mg.) was introduced into a 25-c.c. flask connected with a weighed calcium chloride tube and two carbon dioxide absorption tubes in series; the flask was slowly heated at 105—110° for 2 hours while purified nitrogen was passed through the apparatus. Water (30·3 mg.) and a negligible quantity of carbon dioxide (3·5 mg.) were collected. The gummy acid was completely converted into the lactone (527 mg.), $[\alpha]_D^{20°}$ +81·8° ±1·6° (*c* = 1·26% in ethanol).

Acid hydrolysis of the lactone. The lactone (92 mg.) was hydrolysed with concentrated hydrochloric acid (2 c.c.) in a sealed tube at 125° for 5 hours. From the hydrolysate, D-α-hydroxy*iso*valeric acid (28 mg.), m. p. 65—66°, $[\alpha]_D^{21°}$ −18·2° ±1·7° (*c* = 1·22% in chloroform), and *N*-methyl-L-valine hydrochloride, m. p. 149°, $[\alpha]_D^{21°}$ +17·4° ±2·0° (*c* = 1% in ethanol), were isolated.

Chromatography of the lactone. The lactone (290 mg.) was dissolved in benzene (5 c.c.) and chromatographed on alumina. The eluate yielded a colourless oil (73 mg.) which was apparently the unchanged lactone. When elution was effected with methanol, a hygroscopic solid (132 mg.) was obtained. This substance was apparently the *sodium* salt of the ring-opened lactone (Found: C, 52·1; H, 7·6. $C_{11}H_{20}O_4NNa$ requires C, 52·2; H, 7·9%).

The acid (121 mg.) from an alkaline hydrolysis of lateritiin-I was carefully prepared, care being taken to avoid lactonisation, and allowed to react with excess of ethereal diazomethane. After 2 minutes the ether and excess of diazomethane were removed under reduced pressure, and the resulting oil set aside for 5 minutes, by which time it had set to a mass of crystals (122 mg.). Repeated crystallisations of the product from light petroleum at −10° yielded long colourless needles of the *methyl* ester, m. p. 78°, $[\alpha]_D^{21°}$ −128° ±4° (*c* = 0·43% in chloroform) (Found: C, 58·6; H, 9·5; N, 5·8; active H, 0·39; *M*, cryoscopic in bromoform, 243. $C_{12}H_{23}O_4N$ requires C, 58·8; H, 9·4; N, 5·7; one active H, 0·41%; *M*, 245). The same ester was obtained in exactly similar manner by mild alkaline hydrolysis of sambucinin.

The ester (163 mg.) was dissolved in dry benzene (1·6 c.c.), and 3 : 5-dinitrobenzoyl chloride (152 mg.) added followed by pyridine (0·1 c.c.). The mixture was heated under reflux on the steam-bath for 15 minutes, diluted with ether (20 c.c.), and the ethereal solution shaken first with 0·05N-sulphuric acid (5 c.c.), and then with 1N-sodium hydrogen carbonate solution (5 c.c.). After washing the ether solution with water (3 × 10 c.c.), drying, and evaporating, a gum was obtained which could not be crystallised even after chromatography on acid-washed alumina. The 3 : 5-dinitrobenzoate was therefore dissolved in ether (3 c.c.) and an excess of α-naphthylamine in ether added, whereupon red crystals of the *α-naphthylamine* adduct were deposited (112 mg.). These were recrystallised three times from methanol and gave red, rectangular plates, m. p. 147° (Found: C, 59·7; H, 6·0. $C_{29}H_{34}O_5N_4$ requires C, 59·8; H, 5·8%).

Hydrolysis of the ester (64 mg.) with concentrated hydrochloric acid (1 c.c.) yielded D-α-hydroxy-*iso*valeric acid (21 mg.), m. p. 64—65°, $[\alpha]_D^{22°}$ −17·9° ±2·3° (*c* = 0·78% in chloroform), and *N*-methyl-L-valine hydrochloride (25 mg.), m. p. 147—148°, $[\alpha]_D^{22°}$ ±24·6° ±2·0° (*c* = 1% in ethanol).

The lactone (195 mg.) was dissolved in methanol (3 c.c.) and kept overnight with 2N-sodium hydroxide (1 c.c.) at room temperature. Extraction of the diluted reaction mixture with ether yielded no product, but acidification and extraction afforded a gummy acid which on reaction with diazomethane gave a crystalline ester (155 mg.), m. p. 78°, mixed m. p. 78° (with methyl ester from alkaline hydrolysis of lateritiin-I).

Mild Alkaline Hydrolysis of Fructigenin.—Fructigenin (300 mg.) was dissolved in methanol (5 c.c.) and 1N-sodium hydroxide (5 c.c.) was added. After the mixture had stood for 16 hours at 20°, water (10 c.c.) was added, and methanol removed in a vacuum. The aqueous solution was extracted with ether (2 × 5 c.c.), acidified with 2N-hydrochloric acid, and re-extracted with ether (2 × 10 c.c.). After being washed with water, the solution was dried and excess of diazomethane in ether was added. After standing for 5 minutes, ether was removed in a vacuum, and the residue crystallised on scratching.

Recrystallisation from light petroleum gave colourless needles, m. p. 77°, not depressed on admixture with the compound from lateritiin-I.

Preparation of the Above Lactone and Methyl Ester from L(−)-α-*Bromoisovaleric Acid and* N-*Methyl*-DL-*valine.*—*N*-Methyl-DL-valine (1 g.) was suspended in dry chloroform (25 c.c.), and D(−)-α-bromo*iso*-valeryl chloride (1·5 g.) added, followed by dry pyridine (2 c.c.). The mixture became warm and the solid disappeared; after 10-minutes' shaking, the solvent was removed in a vacuum, leaving a yellow oil. Water (10 c.c.) and pyridine (2 c.c.) were added, and the mixture heated at 100° for 1 hour. It was then cooled, acidified, and extracted with ether (2 × 20 c.c.); the ethereal solution was evaporated in a vacuum and heated at 100° for 1 hour at 15 mm. The gum which resulted was dissolved in ether (20 c.c.) and shaken with 1N-sodium hydroxide (5 c.c.) followed by water (5 c.c.), and the ether removed; a gum (1·5 g.) was obtained, $[\alpha]_D^{20°}$ +52·2° ±2° (*c* = 0·95% in ethanol). This was dissolved in ether and passed through a column (25 cm. × 1 cm.) of acid-washed alumina (pH 4). The total eluate (800 mg.) was kept for several days at 0° and a small amount of crystalline material (m. p. 82°) separated; this was filtered off and found to be optically inactive. The residual oil was the required *lactone*, $[\alpha]_D^{20°}$ +79° ±2° (*c* = 1·0% in ethanol) (Found: C, 61·65; H, 9·0; N, 6·71%. $C_{11}H_{19}O_3N$ requires C, 61·97; H, 8·92; N, 6·57%).

The nature of crystalline material was established by repeating the preparation but using DL-α-bromo*iso*valeryl chloride; after the stage of chromatography on alumina, it was the sole product and is one of the two possible diastereoisomers of the lactone. On using D(+)-α-bromo*iso*valeryl chloride, an oily lactone was obtained, $[\alpha]_D^{20°}$ −78° ±2° (*c* = 0·96% in ethanol); on admixture with an equal amount of the natural lactone, the crystalline material (m. p. 82°) was obtained.

The synthetic lactone ($[\alpha]_D^{20°}$ 79° ±2°) (500 mg.) was dissolved in methanol (5 c.c.) and N-sodium hydroxide (5 c.c.) added. After the mixture had been kept at 20° for 16 hours, water (10 c.c.) was added, and the methanol removed in a vacuum. The solution was extracted with ether (5 c.c.), acidified with hydrochloric acid, re-extracted with ether (2 × 10 c.c.), and dried. Diazomethane in ether was added until the solution remained permanently yellow, and after 10 minutes the solvent was removed in a vacuum. The gummy residue crystallised on scratching and was recrystallised three times from light petroleum (b. p. 40—60°), giving colourless needles, m. p. 75°, not depressed on admixture with the natural *ester*, $[\alpha]_D^{19°}$ −128° ±2° (*c* = 1·0% in chloroform) (Found: C, 58·95; H, 9·35; N, 6·2. $C_{12}H_{23}O_4N$ requires C, 58·78; H, 9·39; N, 5·71%).

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218. *Mechanism and Extension of the Fischer Oxazole Synthesis.*

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A reconsideration of the Fischer oxazole synthesis has led to the preparation of 2 : 5-disubstituted oxazoles from aldehydes and α-hydroxy-amides. Unlike the Fischer synthesis (from aldehydes and α-hydroxy-cyanides) the new method is not limited to diaryloxazoles.

EMIL FISCHER'S synthesis of 2 : 5-diaryloxazoles (*Ber.*, 1896, **29**, 205) involves the condensation, in dry ethereal hydrogen chloride, of an aldehyde with an aldehyde cyanohydrin. The oxazoles, $R{-}C_3HON{-}R'$, are regularly accompanied by substances having the composition $R{-}C_3H_3O_2N{-}R'$; these have usually been regarded as Schiff bases (I) of aldehydes with α-hydroxy-amides.

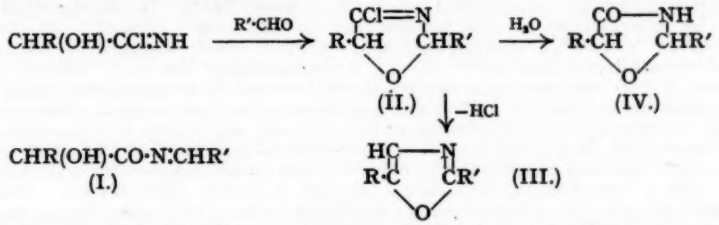
Ingham (*J.*, 1927, 692) studied the reaction of benzaldehyde with mandelonitrile and hydrogen chloride, and showed that when a small proportion of water is added there is only one product, *A* (called benzylidenemandelamide by Ingham), the formation of which can be entirely suppressed by addition of thionyl chloride. He concluded that in the Fischer synthesis compound *A* arises by hydrolysis of an intermediate substance, and suggested a mechanism in which addition of hydrogen chloride to the cyanide was the first step. The resulting iminochloride was presumed to react with benzaldehyde to give CHPh(OH)·CCl:N·CHPh·OH, which could pass to (I; R = R′ = Ph) by hydrolysis and dehydration or to 2 : 5-diphenyloxazole (III; R = R′ = Ph) *via* the intermediate (II; R = R′ = Ph).

The formulation (Michael and Jeanprêtre, *Ber.*, 1892, **25**, 1682) of compound *A* as (I; R = R′ = Ph) was criticised by Staudinger and Ruzicka (*Annalen*, 1911, **380**, 282) who preferred the oxazolidone structure (IV; R = R′ = Ph). It has been shown since that the products obtained by condensing acetone with α-hydroxy-amides are certainly oxazolidones (H. O. L. Fischer, Dangschat, and Stettiner, *Ber.*, 1932, **65**, 1032). We find that compound *A* dissolves easily in aqueous sodium hydroxide, and is recovered on acidification. Acidity in a compound of type (I) would be very surprising, but it is frequently found among cyclic imides.

Moreover, compound *A* is unaffected by boiling with acetyl chloride or with thionyl chloride in ether.

Staudinger and Ruzicka suggested that in the Fischer synthesis the oxazole (III) was produced from the oxazolidone (IV) by loss of water, and there is a paper by Schuster (*J. Pharm. Chim.*, 1936, **23**, 142) which, though ambiguous, appears to suggest that this is actually the case. Compound *A* has now been found to remain unchanged on treatment with ethereal hydrogen chloride; this idea of the mechanism is therefore incorrect.

By adopting the oxazolidone structure for compound *A* it is possible to modify and simplify Ingham's mechanism as follows:



The transformation (II) ⟶ (III) requires the mobilisation of two protons. This would occur more readily, and hence compete more successfully with the simultaneous hydrolysis of (II), if the groups R and R′ are aromatic. In fact, the Fischer synthesis has been successfully applied only to aromatic-type aldehydes and their cyanohydrins; Fischer (*loc. cit.*) condensed benzaldehyde with acetaldehyde cyanohydrin and obtained only the so-called benzylidenelactamide, which is soluble in alkali and hence should be regarded as (IV; R = Me, R′ = Ph).

This modified view of the synthesis suggested that an oxazolidone (IV) might be converted into an oxazole (III). In fact, compound *A* was found to afford 2 : 5-diphenyloxazole in good yield on being warmed with phosphoryl chloride; the chloro-oxazoline (II) is a likely intermediate. This new oxazole synthesis proved to be of more general application than the Fischer method. Benzaldehyde and lactamide were condensed by boiling in toluene with a little toluene-*p*-sulphonic acid. Fractionation of the acidic product gave a substance apparently identical with that obtained by Fischer and a product which had the same composition but was still not homogeneous. The oxazolidones (IV) should exist in *cis*- and *trans*-forms, and both of these were probably present. The total product on warming with phosphoryl chloride afforded 2-phenyl-5-methyloxazole.

Lactamide and *n*-heptaldehyde were also condensed. The oily acidic product, obtained in poor yield, was converted by phosphoryl chloride into *5-methyl-2-n-hexyloxazole*; somewhat better results were obtained by treating the total condensation product, which was mainly neutral, with phosphoryl chloride. It is possible that, with this oxazolidone, ring-chain tautomerism occurs (I ⇌ IV); such tautomerism has been noted in certain oxazolidines (Cope and Hancock, *J. Amer. Chem. Soc.*, 1942, **64**, 1503; 1944, **66**, 1453).

Experimental.

Stability of Compound A (*2 : 5-Diphenyloxazolid-4-one*).—The substance (0·4 g.) was suspended in dry ether (100 c.c.) and dry hydrogen chloride passed in until the solution was saturated. The solid largely dissolved, and after some hours the ether was evaporated. The solid residue had m. p. 194—196° after crystallisation from alcohol, and was unchanged compound *A*. No indication of oxazole formation was found.

2 : 5-Diphenyloxazole.—Compound *A* was prepared by passing hydrogen chloride into moist ether containing equimolar amounts of benzaldehyde and mandelonitrile. The product (2 g.; m. p. 190°; not recrystallised) was warmed with phosphoryl chloride (10 c.c.) for half an hour at 85—90°. After phosphoryl chloride had been removed at low pressure the solid residue was triturated with 1% ethereal hydrogen chloride, collected (2·6 g.), and shaken with water and ether. The dried ethereal layer on evaporation left nearly pure 2 : 5-diphenyloxazole (1·5 g.), m. p. 65—67° raised to 70—71° by crystallisation from light petroleum (Found: N, 6·6. Calc. for $C_{15}H_{11}ON$: N, 6·3%). The *picrate* separated from alcohol in small yellow needles, m. p. 172—173° (Found: N, 12·6. $C_{15}H_{11}ON,C_6H_3O_7N_3$ requires N, 12·4%).

Lactamide.—Ethyl lactate (100 g.) and a saturated solution (200 c.c.) of ammonia in methanol were placed in a bottle and kept at 37° for 20 hours. After solvent had been evaporated (finally at 100°/20 mm.), the residue was recrystallised from ethyl acetate, giving lactamide (65·3 g.; 87%), m. p. 73—74°.

2-Phenyl-5-methyloxazolid-4-one (*so-called Benzylidenelactamide*).—Lactamide (5 g.), benzaldehyde (6 g.), and toluene-*p*-sulphonic acid (0·15 g.) in dry toluene (80 c.c.) were heated under reflux in a Soxhlet apparatus (thimble filled with anhydrous potassium carbonate) for 14 hours. Next day the long needles (4 g.) were separated from the toluene, and washed with light petroleum. This product had m. p.

122—125°, and on recrystallisation from water gave Fischer's so-called benzylidenelactamide, m. p. 129—130°, which (m. p. 129—131°) was also obtained from benzaldehyde, lactamide, and ethereal hydrogen chloride. The toluene filtrate was extracted with sodium hydroxide (25 c.c.; 2N.), and the extract treated with charcoal and acidified. The partly oily precipitate was treated again in alkaline solution with charcoal and carefully precipitated by acid. The colourless crystalline product (2·7 g.) softened at 60°; the melt was still turbid at 90° (Found: C, 67·7; H, 6·3; N, 7·6. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%). Fractional crystallisation from light petroleum failed to give a homogeneous product.

2-Phenyl-5-methyloxazole.—The above oxazolidone (2 g.; high- or low-melting material) was warmed with phosphoryl chloride (10 c.c) for 15 minutes at 80—85°. Most of the phosphoryl chloride was removed at low pressure; the residue was made strongly alkaline and distilled in steam. The volatile oil, collected by means of ether, was distilled (0·5 g.; b. p. about 245°). It was identified as 2-phenyl-5-methyloxazole by comparison of the picrate, m. p. 145—146° (Found: N, 14·3. Calc. for $C_{10}H_9ON,C_6H_3O_7N_3$: N, 14·7%), with an authentic specimen kindly supplied by Dr. D. F. Elliott.

5-Methyl-2-n-hexyloxazole.—Lactamide (20 g.), *n*-heptaldehyde (40 c.c.), toluene (150 c.c.), and glacial acetic acid (4 c.c.) were heated under reflux for 16 hours in an apparatus which automatically separated water from the condensate. The toluene solution, after being washed with water and aqueous sodium hydrogen carbonate, was concentrated at low pressure, and excess of heptaldehyde removed at 100°/20 mm. The residue (38 g.) was heated with phosphoryl chloride (100 c.c.) at 90—95° for half an hour, and then, after removal of phosphoryl chloride, was steam-distilled from its alkaline solution. The volatile oil (13·5 g.) was distilled, and gave a fraction, b. p. 220—235° (6·4 g.). The crude oxazole (1 g.) was treated with mercuric chloride (1·6 g.) in alcohol (6 c.c.), and water (3 c.c.) was added. The oily precipitate soon crystallised. A sample (1 g.) was purified by dissolution in ether (4 c.c.), slow addition of light petroleum (b. p. 40—60°; 3 c.c.), filtration, and addition of more light petroleum (1 c.c.). *5-Methyl-2-n-hexyloxazole mercurichloride* crystallised in glistening rhombic plates, m. p. 65—67° (Found: C, 27·8; H, 3·8. $C_{10}H_{17}ON,HgCl_2$ requires C, 27·4; H, 3·9%). Steam distillation of the mercurichloride gave the free base, which was collected by means of light petroleum, heated with solid potassium hydroxide, and distilled. The *5-methyl-2-n-hexyloxazole* was a colourless oil of powerful and peculiar odour; b. p. 213°/765 mm.; $n_D^{17°}$ 1·4520 (Found: C, 71·3; H, 10·3. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%). The picrate and hydrochloride were oily. A *picrolonate* was obtained by dissolving the base (0·13 g.) and picrolonic acid (0·1 g.) in acetone, concentrating to small bulk, and adding alcohol. The long yellow needles sintered at 62° and melted at 97° (decomp.); they appeared to be solvated (Found: C, 56·5; H, 7·0; N, 14·7. $C_{10}H_{17}ON,C_{10}H_8O_5N_4,C_3H_6O$ requires C, 56·4; H, 6·4; N, 14·3%).

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219. *The Isomerisation of Dienœstrol and Some Related Dienes and Indenes.*

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Dienœstrol and some related dienes have been found to undergo cyclisation to the corresponding indenes under mild acid conditions. During the preparation of the dienes from the respective pinacols by dehydration with acetic anhydride–acetyl chloride mixtures the same indenes were also found to be formed in addition to the dienes.

DURING experiments on the metabolism of dienœstrol (Sahasrabudhe and Wilder Smith, *Biochem. J.*, 1947, **41**, 190; Hausmann and Wilder Smith, *Nature*, 1948, **161**, 892) unaccountable losses of œstrogenic activity were noticed when urines containing free added dienœstrol were heated under reflux in the presence of dilute mineral acids. In order to eliminate the possibility that such losses were due to interference by unknown factors in the urine or to oxidation, an aqueous suspension of dienœstrol, 1N. with respect to hydrochloric acid, was heated under reflux for 1 hour in a stream of nitrogen. From the resultant suspension, an 80% yield of an isomer, m. p. 175—176°, was isolated which proved to be identical with the œstrogen obtained by Adler and Hägglund (*Arkiv Kemi, Min., Geol.*, 1945, **19**, *A*, No. 23) by the action of boron trifluoride on dienœstrol in chloroform solution and which they designated "Indenœstrol A." This indene, 4′: 6-dihydroxy-2-phenyl-1-methyl-3-ethylindene, has an E.D. 50 of approximately 3 μg. when tested on spayed rats by the technique used at this Institute (Wilder Smith and Williams, *J. Endocrin.*, 1947, **5**, 152). Under the same conditions dienœstrol has an E.D. 50 of about 0·7 μg., so this transformation would account for the observed losses of œstrogenic potency.

It has been found that other dilute mineral acids, such as sulphuric and phosphoric acids, are able to effect the same cyclisation under the same conditions. Also, passage of dry hydrogen chloride into a solution of dienœstrol in glacial acetic acid in the cold, or the addition of a trace of concentrated sulphuric acid to such a solution, gave a good yield of the same isomer.

Similar isomerisations occur in other suitably substituted dienes. For example, treatment of 3 : 4-diphenylhexadiene with dry hydrogen chloride in hot glacial acetic acid solution yielded 2-phenyl-1-methyl-3-ethylindene. As would be expected, the same indene was formed during the preparation of 3 : 4-diphenylhexadiene by dehydration of propiophenone pinacol with a mixture of acetyl chloride and acetic anhydride. Plentl and Bogert (*J. Amer. Chem. Soc.*, 1941, **63**, 989) have synthesised 2-phenyl-3-methyl-1-ethylindene from 2-phenyl-3-methylindan-1-one. They describe it as a bright orange viscous oil distilling under reduced pressure, but do not state a boiling point or pressure. They give, however, a correct analysis. Our material (m. p. 46—47°), on catalytic reduction in the presence of palladium charcoal, showed one reducible double bond per molecule, and on analogy with the cyclisation to the other indenes described it is assumed to be 2-phenyl-3-methyl-1-ethylindene, which would agree with the properties quoted by Plentl and Bogert (*loc. cit.*). 2 : 3-Diphenylbutadiene and acetophenone pinacol yielded 2-phenyl-3-methylindene under similar conditions.

The latter observation would explain the findings of Allen, Eliot, and Bell (*Canadian J. Res.*, 1939, **17**, 75), *viz.*, that a substance, m. p. 69—73°, was formed during the dehydration of acetophenone pinacol, but they did not identify it. 2-Phenyl-3-methylindene melts at 75—76°.

The type of cyclisation reported here would also explain the anomalies observed by Campbell and Chattaway (*Proc. Roy. Soc.*, 1942, *B*, **130**, 435), who dehydrated four pinacols with acetic anhydride–acetyl chloride mixtures and found that the resultant " dienes " only absorbed half or less of the theoretical amounts of hydrogen on catalytic reduction.

Blum-Bergmann (*Ber.*, 1932, **65**, 109; *J.*, 1935, 1020) observed that the dehydration of certain pinacols with dilute mineral acid yielded the corresponding indenes. However, propiophenone pinacol, when heated for 5 hours with 1N-hydrochloric acid, yielded no appreciable amounts of indene or diene.

Ziegler and Sauermilch (*Ber.*, 1930, **63**, 1856) found that certain phenyl-substituted allenes isomerised to the corresponding indenes in the presence of mineral acids. Dienœstrol, containing two *p*-hydroxy-phenolic groups, cyclised more readily than the corresponding hydrocarbon.

Catalytic reduction of indenœstrol A gave two isomeric indanes. The higher-melting isomer, m. p. 198—199° (decomp.), as described by Adler and Hägglund (*loc. cit.*), was comparatively inactive biologically (E.D. 50 about 200 μg.). The lower-melting *isomer* (m. p. 74°) showed about the same biological activity as the original indene (E.D. 50 about 3 μg.) and has, as far as we are aware, not been described before.

Experimental.

Cyclisation of Dienœstrol in Aqueous Medium.—Dienœstrol (2 g.), on being heated under reflux for 1 hour in 1N-hydrochloric acid in a stream of nitrogen, became greenish-yellow and then deposited a white precipitate after about 20 minutes. After being cooled to 0°, the product (1·88 g.) was filtered off, washed with water until neutral, treated with charcoal and acetone, and crystallised from acetone–benzene to yield a white microcrystalline powder (1·23 g.), m. p. 175—176° (Adler and Hägglund, *loc. cit.*, quote 175°). The powder readily aquired electrostatic charges which made it difficult to handle (Found : C, 80·9; H, 6·9. Calc. for $C_{18}H_{18}O_2$: C, 81·2; H, 6·8%).

The same indene was obtained in excellent yield and purity when 1N-sulphuric or -phosphoric acid was employed under the same conditions. Treatment with water only or with dilute acetic acid did not effect any cyclisation.

Cyclisation of Dienœstrol in a Non-aqueous Medium.—Dienœstrol (5 g.) in glacial acetic acid (200 ml.) was cooled to 30°, and a vigorous current of dry hydrogen chloride passed through the solution during 20 minutes. The mixture became dark green. After 40 minutes' keeping at 0°, the solvent was evaporated in a stream of nitrogen under reduced pressure, and the viscous oily residue solidified on cooling. Three crystallisations from acetone–benzene yielded the indene as before, m. p. 175—176° (3·3 g.).

A similar experiment using one drop of concentrated sulphuric acid instead of hydrogen chloride gave the same product in 82% yield. Concentrated (90%) phosphoric acid under the same anhydrous conditions in the cold left dienœstrol unchanged, but cyclisation occurred readily on 1 hour's refluxing (62% yield). Refluxing dienœstrol for 1 hour in glacial acetic acid effected no noticeable cyclisation.

Characterisation of 4′ : 6-Dihydroxy-2-phenyl-1-methyl-3-ethylindene (Indenœstrol A).—On warming, the indene dissolved in 2N-aqueous sodium carbonate to give a yellow solution. It could not be recovered quantitatively by acidification and ether extraction. No addition compound with maleic anhydride could be formed under the conditions required for reaction in the case of the isomeric dienœstrol (Sahasrabudhe and Wilder Smith, *loc. cit.*).

Reduction to the Indanes.—4′ : 6-Dihydroxy-2-phenyl-1-methyl-3-ethylindene (200 mg.) in absolute ethanol (10 ml.) was catalytically reduced (at 760 mm. and 20°) with hydrogen and 2% palladium–charcoal (100 mg.), 1 mole of hydrogen (18·5 ml.) being absorbed in 2 hours. Filtration and the addition of water to the filtrate yielded a product (150 mg.) as colourless needles, m. p. 198—199° (decomp.), after three crystallisations from benzene–light petroleum (b. p. 60—80°) (Found : C, 80·7; H, 7·5.

Calc. for $C_{18}H_{20}O_2$: C, 80·6; H, 7·5%) (Adler and Hägglund, *loc. cit.*, quote m. p. 196—197°). The E.D. 50 was about 200 μg. in spayed rats.

From the mother-liquor an isomeric *indane* crystallised in long, colourless needles, m. p. 74°, on the addition of more light petroleum (b. p. 60—80°) (Found: C, 80·6; H, 7·6. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%). The E.D. 50 in spayed rats was about 3 μg.

Diacetate. The indene (200 mg.), acetic anhydride (400 mg.), and pyridine (3 ml.) were heated on the steam-bath for 2 hours. After working up and recrystallising from benzene–light petroleum (b. p. 60—80°), the diacetate was obtained as colourless needles (120 mg., 60%), m. p. 150—151° (Adler and Hägglund, *loc. cit.*, give for their indenœstrol diacetate m. p. 150—151°) (Found: C, 75·4; H, 6·4. Calc. for $C_{22}H_{22}O_4$: C, 75·4; H, 6·3%).

Dibenzoate. 4′:6-*Dibenzoyloxy*-2-*phenyl*-1-*methyl*-3-*ethylindene* was prepared from the indene, benzoyl chloride, and pyridine, and after three crystallisations from benzene–light petroleum (b. p. 60—80°) was obtained as colourless needles, m. p. 176—177° (Found: C, 81·1; H, 5·7. $C_{32}H_{26}O_4$ requires C, 81·0; H, 5·5%).

The corresponding *di*-p-*nitrobenzoyloxy*-derivative was prepared from the indene, *p*-nitrobenzoyl chloride, and pyridine, and after three crystallisations a yellowish microcrystalline powder, m. p. 201—203°, was obtained (Found: N, 5·0. $C_{32}H_{24}O_8N_2$ requires N, 5·0%).

Cyclisation of 2:3-*Diphenylbutadiene.*—The butadiene (3·7 g.), m. p. 45—47° (Allen *et al.*, *loc. cit.*), in glacial acetic acid solution (50 ml.) was treated for 5 minutes with a rapid stream of dry hydrogen chloride and then heated under reflux for 5 hours; a green colour developed almost immediately. After removal of the solvent under reduced pressure, the residue was distilled to give two fractions: (1) b. p. 116—130°/0·3 mm. (1·55 g.), containing chiefly unchanged butadiene; (2) b. p. 130—135°/0·3 mm. (1·27 g.), m. p. 76—77°, after two crystallisations from methanol (Found: C, 93·0; H, 6·9. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). Hydrogenation at 760 mm. and 20° in ethanol in the presence of 2% palladium–charcoal showed the presence of one reducible double bond per molecule. Blum-Bergmann (*loc. cit.*) and Allen *et al.* (*loc. cit.*) quote m. p. 76—78° and 75—76°, respectively.

2-*Phenyl*-3-*methylindene from Acetophenone Pinacol.*—The pinacol, b. p. 150°/0·1 mm. (32·8 g.), acetyl chloride (81 ml.), and acetic anhydride (120 ml.) were heated under reflux for 2 hours, and the solvents removed under reduced pressure. To the resultant oil, 5 vols. of hot methanol were added, and the solution filtered after being heated under reflux for 5 minutes. On cooling, some crystals and a tar separated which were filtered off, treated with charcoal and crystallised twice from methanol. White needles, m. p. 76—77° (3·9 g.), were obtained which showed no m. p. depression with 2-phenyl-3-methylindene. From the mother-liquors a somewhat viscous yellow oil was obtained, b. p. 124—129°/0·05 mm. (10·1 g.), which yielded a further 2·3 g. of the same indene on crystallisation from methanol.

2-*Phenyl*-3-*methylindane.*—2-Phenyl-3-methylindene (1·5 g.) in ethanol (50 ml.) in the presence of 2% palladium–charcoal (100 mg.) at 760 mm. Hg and 20° absorbed 169 ml. of hydrogen in 2 hours (theory for 1 mole, 163 ml.). After removal of the catalyst and the solvent, the residue was distilled to give 2-*phenyl*-3-*methylindane* as a colourless oil, b. p. 106°/0·4 mm. (1·23 g.) (Found: C, 92·0; H, 7·7. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%).

Cyclisation of 3:4-*Diphenylhexadiene.*—The hexadiene, m. p. 100—101° (8·2 g.), was suspended in glacial acetic acid (70 ml.) and saturated with dry hydrogen chloride during 15 minutes, then heated under reflux for 1 hour. After resaturation with hydrogen chloride and refluxing for 1 hour, the solvent was removed under reduced pressure. Unchanged diphenylhexadiene was removed by addition of maleic anhydride (10 g.) and xylene (50 ml.) followed by refluxing for 30 minutes. The cooled solution was extracted twice with 50 ml. portions of water, then three times with 50 ml. portions of 2N-sodium hydroxide; the solvent was removed, and the residue distilled under reduced pressure to give a main fraction, b. p. 122—124°/0·05 mm. (5·73 g.), an orange viscous oil. On standing for one month the oil crystallised. After three crystallisations from methanol white plates were obtained, m. p. 46—47° to a colourless oil [Found: C, 92·1; H, 7·8; *M* (Rast), 218. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%; *M*, 234].

The same substance was isolated from the mother-liquors remaining after the preparation of 3:4-diphenylhexadiene from propiophenone pinacol: this pinacol (33·2 g.), b. p. 150°/0·05 mm., yielded after 2 hours' refluxing with acetyl chloride (81 ml.) and acetic anhydride (120 ml.), 3:4-diphenylhexadiene, m. p. 100—101° (14·0 g.; 49%), and 2-phenyl-3-methyl-1-ethylindene, b. p. 128°/0·1 mm. (8·2 g.; 28%).

2-*Phenyl*-3-*methyl*-1-*ethylindane.*—The indene (2·13 g.) and ethanol (50 ml.) in the presence of 2% palladium–charcoal (100 mg.) at 760 mm. and 20° absorbed 209 ml. of hydrogen (theory for one double bond, 204 ml.) in 4 hours. One removal of the catalyst and the solvent, 2-*phenyl*-3-*methyl*-1-*ethylindane* remained as an oil which was distilled under reduced pressure, b. p. 115—116°/0·3 mm. (1·32 g.), as an almost colourless, somewhat viscous oil (Found: C, 91·2; H, 8·5. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%).

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220. *Studies on Hydrogen Cyanide. Part XVI. The Constitution of the "Sesquichloride."*

By Leonard E. Hinkel and Roy P. Hullin.

The view previously expressed by Hinkel and Watkins (*J.*, 1944, 647) on the constitution of the sesquichloride of hydrogen cyanide has been supported by a study of its aluminium chloride compounds. The sesquichloride unites with two molecules of aluminium chloride yielding a product which reacts with benzene in the presence of free aluminium chloride, giving rise to a mixture of diphenylmethane, anthracene, and triphenylcarbinol with only a small amount of benzhydrylformamidine hydrochloride.

By reaction between the sesquichloride of hydrogen cyanide and benzene in the presence of free aluminium chloride, Gattermann and Schnitzpahn (*Ber.*, 1898, **31**, 1770) obtained the hydrochloride of benzhydrylformamidine (I), and consequently assigned to the sesquichloride the structure of dichloromethylformamidine hydrochloride (II).

$CHPh_2 \cdot NH \cdot CH{:}NH$ (I.) $CHCl_2 \cdot NH \cdot CH{:}NH,HCl$ (II.)

Hinkel and Watkins (*loc. cit.*), in studying the action of hydrogen chloride on hydrogen cyanide, considered that the sesquichloride results as a union between formimidochloride and formamidodichloride, and therefore regarded the sesquichloride as chloro-*N*-(dichloromethyl)methylenediamine (III).

$$CHCl{:}NH + CHCl_2 \cdot NH_2 \longrightarrow CHCl_2 \cdot NH \cdot CHCl \cdot NH_2 \quad \text{(III.)}$$

Evidence in support of this view has now been obtained through a further study of the action of aluminium chloride on the sesquichloride in the presence of benzene. Aluminium chloride readily combines with 1 mol. of the sesquichloride (Hinkel, Ayling, and Beynon, *J.*, 1935, 674), and the compound so formed reacts slowly with toluene in the presence of free aluminium chloride yielding as final product the tolylhydrylamine but only in 84% yield, whereas the uncombined sesquichloride reacts vigorously and almost quantitatively with toluene in the presence of free aluminium chloride.

The above additive compound of aluminium chloride with the sesquichloride readily unites with a further molecule of aluminium chloride on heating, and at the same time a remarkable change occurs within the molecule. The dark product does not solidify on cooling but, unlike the above mono-derivative, reacts vigorously with benzene in the presence of free aluminium chloride yielding diphenylmethane, anthracene, and triphenylcarbinol together with only a small amount of the expected benzhydrylformamidine hydrochloride.

It would appear that the additional molecule of aluminium chloride has caused the sesquichloride molecule to undergo incipient or partial disruption into active fragments, which in the presence of free aluminium chloride unite with the benzene; thus, in the reaction mixture before hydrolysis, the characteristic odour of diphenylmethane can readily be detected. The diphenylmethane and also the anthracene, unlike the triphenylcarbinol, cannot be hydrolysis products.

The formation of anthracene and triphenylcarbinol is highly significant since these compounds indicate the presence of $\cdot NH \cdot CHCl \cdot NH_2$ in the original molecule, thus giving support to the constitution (III).

It is evident that at one stage, either before or after partial disruption, the halogens on the carbon atom must have reacted with benzene under the influence of the free aluminium chloride giving rise to the completely and the partly disrupted fragment, $CHPh{:}$ and $\cdot NH \cdot CHPh \cdot NH_2$. It is highly probable that the anthracene owes its origin to a union of 2 mols. of the benzylidene fragments. In the second case, the fragment $\cdot NH \cdot CHPh \cdot NH_2$ would probably be in combination with the aluminium chloride through one of the nitrogen atoms, and reacting further with benzene under the influence of free aluminium chloride, would yield a complex with the latter which on hydrolysis affords triphenylcarbinol.

It is not necessary to unite the sesquichloride with the 2 moles of aluminium chloride before reaction with benzene, since the same results as above can be obtained when the sesquichloride is added slowly to a large excess of powdered aluminium chloride suspended in benzene at 0°.

Experimental.

Preparation of $2AlCl_3,2HCN,3HCl$.—Finely-powdered aluminium chloride (67 g.; 1 mol.) and the sesquichloride of hydrogen cyanide (82 g.; 1 mol.) were intimately mixed and gently heated in a flask protected from moisture until reaction set in; the mixture soon became molten, and on cooling, a white

solid mass, m. p. 62°, was obtained. To the molten mass was gradually added more finely-divided aluminium chloride (67 g.; 1 mol.), the mixture being warmed on a water-bath after each addition to aid solution and combination. After complete addition, the dark mixture was heated for a further 5 minutes, and the liquid decanted from any unchanged solid and allowed to cool in a desiccator. It did not solidify even after some hours.

Reaction of $2AlCl_3,2HCN,3HCl$ *with Benzene.*—The compound prepared above was added in small portions to benzene (300 c.c.) containing powdered aluminium chloride (33·5 g.; 0·5 mol.), mechanically stirred and cooled externally with ice. A vigorous reaction ensued after each addition, hydrogen chloride being evolved; the temperature of the mixture was maintained at 0° during the addition and for several hours afterwards. The deep red benzene solution obtained when the mixture regained room temperature was poured into a mixture of concentrated hydrochloric acid and crushed ice. The benzene layer was separated, the aqueous layer shaken with two further portions of benzene (100 c.c.), and the extracts combined.

Treatment of the benzene layer. The benzene solution was steam-distilled until no more oily drops appeared in the distillate (several hours). The aqueous distillate was extracted with benzene, and the latter separated and dried. Removal of the benzene by distillation yielded diphenylmethane (16 g.) which deposited a little anthracene (0·7 g.) on cooling; the diphenylmethane was obtained by extraction with light petroleum and repeated freezings as a white solid, m. p. 23° unchanged on admixture with an authentic specimen.

The semi-solid (44 g.) in the steam-distillation flask, which consisted of triphenylcarbinol and anthracene, was extracted with light petroleum (b. p. 40—60°), in which the anthracene is only slightly soluble. Repeated crystallisations of the soluble portion from light petroleum (b. p. 60—80°) yielded triphenylcarbinol, which was finally crystallised from aqueous alcohol, from which it separated in iridescent plates, m. p. 164·5°, unchanged on admixture with an authentic specimen.

The combined, more insoluble residues from all the light petroleum extractions, consisting of anthracene, were crystallised from benzene–light petroleum (b. p. 40—60°) and finally from benzene–alcohol. Anthracene was obtained as glittering plates with a strong blue fluorescence; m. p. and mixed m. p. with pure anthracene 216·5°.

Treatment of the aqueous layer. The aqueous layer was concentrated until aluminium chloride crystals began to separate together with a small amount of a black semi-solid. This semi-solid was collected by filtration after sufficient water had been added just to dissolve the aluminium chloride, and was then boiled with aqueous sodium hydroxide until the evolution of ammonia ceased; on cooling, a brown solid was obtained (4 g.). This was a mixture of formobenzhydrylamide and benzhydrylamine which was separated by treatment with ether, in which the former is insoluble. The formobenzhydrylamide was purified by crystallisation from alcohol and was obtained as colourless crystals, m. p. 132° (identity confirmed by mixed m. p. and comparison with an authentic specimen). The benzhydrylamine in the ether extract was acetylated with acetic anhydride after removal of the ether, and the acetobenzhydrylamide, after crystallising several times from alcohol, melted at 146° unchanged on admixture with an authentic specimen.

UNIVERSITY COLLEGE OF SWANSEA. [*Received, September 27th,* 1948.]

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221. *Cyanamides. Part I. The Synthesis of Substituted Arylsulphonylcyanamides.*

By FREDERICK KURZER.

The interaction of aromatic sulphonyl chlorides with arylureas in pyridine at low temperatures has been found to result in the formation of arylsulphonylcyanamides of the type $R{\cdot}SO_2{\cdot}NR'{\cdot}CN$. The reaction is favoured by the presence of a large excess of sulphonyl chloride, nearly theoretical yields of the products then being obtained. A number of arylsulphonylcyanamides has been prepared by this new method and their structure confirmed by an alternative synthesis.

THE action of arylsulphonyl chlorides on urea, first studied by Elander (*Bull. Soc. chim.*, 1880, **34**, 207), was investigated in some detail by Remsen and Garner (*Amer. Chem. J.*, 1901, **25**, 175), who found that benzenesulphonyl chloride and urea, when heated to 100°, react violently to form dicyandiamide benzenesulphonate. The interaction of sulphonyl chlorides with ethyl*iso*urea produces sulphonylethyl*iso*ureas, $Ar{\cdot}SO_2{\cdot}N{:}C(OEt){\cdot}NH_2$, converted by hydrolysis into sulphonylureas, $Ar{\cdot}SO_2{\cdot}NH{\cdot}CO{\cdot}NH_2$ [Cox and Raymond, *J. Amer. Chem. Soc.*, 1941, **63**, 300; Cox, *J. Org. Chem.*, 1942, **7**, 307 (available in this country in abstract only)]. Unsuccessful attempts to obtain arylsulphonylureas directly from sulphonyl chlorides and urea were reported by Haak (G.P. 741,533, 1943) in connection with work on sulphonamides of chemotherapeutic value. Passing mention was made of the formation of sulphonic acids, together with products derived from urea by dehydration and polymerization, such as dicyandiamide, but no details were given. In marked contrast, arylsulphonylguanidines can be synthesized readily from the appropriate sulphonyl chloride and guanidine under various conditions (Marshall *et al.*, *Johns Hopkins Hosp. Bull.*, 1940, **67**, 163; Backer and Moed, *Rec. Trav. chim.*, 1947, **66**, 335).

The present investigation has shown that sulphonyl chlorides react with arylureas at low temperatures to produce substituted sulphonylcyanamides of general formula (IV). The reaction is best carried out by treating 1 mol. of the arylurea, dissolved or suspended in pyridine, with 3 mols. of the sulphonyl chloride, the temperature being kept below 30°. With the excess of sulphonyl chloride employed, the arylurea usually undergoes complete reaction. In this way phenyl-, *p*-tolyl-, *p*-methoxyphenyl-, and 1-*naphthyl-benzenesulphonylcyanamide*, *phenyl-*, p-*tolyl-*, p-*methoxyphenyl-*, and 1-*naphthyl-toluene*-p-*sulphonylcyanamide*, and *phenyl-*, and 1-*naphthyl*-p-*nitrobenzenesulphonylcyanamide* were obtained. Owing to the ease with which the reaction takes place, the presence of groups such as hydroxyl which normally interact with acid halides does not interfere with its general course. Thus, *p*-hydroxyphenylurea when treated with toluene-*p*-sulphonyl chloride for longer periods reacted with simultaneous esterification of the phenolic hydroxyl, giving *toluene*-p-*sulphonyltoluene*-p-*sulphonyloxyphenylcyanamide*. Benzenesulphonylcyanamides have previously been prepared by the action of cyanogen bromide on a number of benzenesulphonanilides (II) in the presence of sodium ethoxide (von Braun, *Ber.*, 1904, **37**, 2809). The substances synthesized by the present method were identical in all respects with specimens prepared by von Braun's procedure, and the structure of the products was further established by a second independent synthesis: phenylcyanamide (III) reacted, in pyridine solution, with benzene-, *p*-toluene- and *p*-nitrobenzenesulphonyl chlorides, to yield benzenesulphonyl-, toluene-*p*-sulphonyl-, and *p*-nitrobenzenesulphonyl-phenylcyanamide, respectively, which proved identical with the compounds obtained from phenylurea.

$$\begin{aligned} &Ph\cdot SO_2\cdot NHR' \text{ (II.)} \longrightarrow Ph\cdot SO_2\cdot NNaR' + CN\cdot Br \longrightarrow Ph\cdot SO_2\cdot NR'\cdot CN \text{ (IV.)} + NaBr \\ &R\cdot SO_2Cl + NHPh\cdot CN \text{ (III.)} \longrightarrow R\cdot SO_2\cdot NPh\cdot CN \text{ (IV.)} + HCl \end{aligned}$$

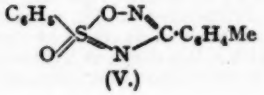
The mechanism of the synthesis of sulphonylcyanamides from arylureas and sulphonyl chlorides involves probably the intermediate formation of arylsulphonylureas (I), which are immediately dehydrated by the excess of sulphonyl chloride and rearrange to form substituted sulphonylcyanamides (IV). The sulphonyl chloride acting as dehydrating agent is itself converted into the corresponding sulphonic acid, the presence of which may be demonstrated by cooling the reaction mixture to 0°, whereupon direct crystallization of a pyridinesulphonic acid salt occurs. The yields of sulphonylcyanamide increase regularly with the use of greater molecular proportions of sulphonyl chloride (cf. table, p. 1036) because increasingly larger quantities of the reagent are made available for the purpose of dehydrating the intermediate.

$$R\cdot SO_2Cl + \overset{3}{N}H_2\cdot CO\cdot \overset{1}{N}HR' \longrightarrow \underset{\text{(I.)}}{R\cdot SO_2\cdot NH\cdot CO\cdot NHR'} \xrightarrow{R\cdot SO_2Cl} \underset{\text{(IV.)}}{R\cdot SO_2\cdot NR'\cdot CN} + R\cdot SO_2\cdot OH + HCl$$

The expectation that arylsulphonylureas, synthesized by alternative methods, might be dehydrated readily by arylsulphonyl chlorides under the mild conditions described has so far not been realized. The ease with which water is eliminated from the intermediate compound in the present synthesis may therefore be restricted to the instant of its formation. Alternatively, the sulphonyl chloride may indeed substitute the hydrogen atom attached to the nitrogen N^1, forming an intermediate $R\cdot SO_2\cdot \overset{1}{N}R'\cdot CO\cdot \overset{3}{N}H_2$, from which the sulphonylcyanamide could be formed directly, and in which case a rearrangement need not be postulated. Backer and Moed (*loc. cit.*), however, have recently shown that arylsulphonyl chlorides, although reacting readily with *p*-nitrobenzenesulphonylguanidine, fail to do so with the corresponding N^3-dimethyl derivative, $NO_2\cdot C_6H_4\cdot SO_2\cdot NH\cdot C(:NH)\cdot NMe_2$, and this observation makes the latter view less probable. Further work on the dehydration of arylsulphonylureas is in progress.

The hydrolytic fission of sulphonylcyanamides proceeds in the expected manner. Treatment with ammonia in the cold results in their conversion into the corresponding substituted sulphonamide, and hydrolysis under more severe condition produces, in addition, the appropriate sulphonic acids and arylureas. For example, toluene-*p*-sulphonylphenylcyanamide gave toluene-*p*-sulphonanilide, m. p. 103°, together with varying quantities of phenylurea and diphenylurea, according to the conditions of the reaction. Hydrolytic conversion into urea is well known in the case of cyanamide itself, and is no doubt preceded, in the present case, by intermediate hydrolysis to phenylcyanamide:

$$\underset{\displaystyle SO_2\cdot R'}{\overset{|}{R\cdot NH}} \longleftarrow \underset{\displaystyle SO_2R'}{\overset{|}{R\cdot N\cdot CN}} \longrightarrow [R\cdot NH\cdot CN] \longrightarrow R\cdot NH\cdot CO\cdot NH_2 \qquad \text{(IV.)} \quad + R'\cdot SO_2\cdot OH$$



(V.)

The synthesis of sulphonylcyanamides by the present method has occasioned the re-examination of the action of benzenesulphonyl chloride upon *p*-toluamidoxime, $CH_3 \cdot C_6H_4 \cdot C(:NH) \cdot NH \cdot OH$. Pinnow (*Ber.*, 1891, **24**, 4167, 4173), when treating a chloroform suspension of this amidoxime with benzenesulphonyl chloride in the presence of alkali, obtained *p*-tolylurea, together with a compound $C_{14}H_{12}O_2N_2S$ [" anhydro-(*p*-toluene amidoxime)-benzenesulphonate "] to which structure (V) was assigned. Its reported physical constants, and the simultaneous formation of *p*-tolylurea, suggested that the product was in fact benzenesulphonyl-*p*-tolylcyanamide. Repetition of Pinnow's work gave small yields of a substance, $C_{14}H_{12}O_2N_2S$, m. p. 91—92°, which showed no depression of the melting point in admixture with benzenesulphonyl-*p*-tolylcyanamide prepared by the above method. The formation of this compound from *p*-toluamidoxime involves presumably a preliminary isomerization to *p*-tolylurea, as shown by its isolation from the reaction mixture, followed by interaction with the excess of sulphonyl chloride in the manner shown above.

The scope and limitations of the present synthesis are being further investigated, particularly with regard to its applicability to *ortho*-substituted derivatives which v. Braun failed to prepare by the cyanogen bromide method. Work on the interaction of sulphinyl chlorides and aliphatic sulphonyl chlorides with arylureas is also in progress.

Experimental.

(Melting points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford.)

Benzenesulphonylphenylcyanamide.—(a) *From phenylurea.* To a solution of phenylurea (13·6 g.; 0·1 mol.) in pyridine (50 ml.), benzenesulphonyl chloride (35 g., *i.e.*, 28 c.c., 0·2 mol.) was added within 3 minutes with external cooling, the temperature of the mixture being kept below 30°. After 10 minutes' standing, the liquid was poured into ice-water (400 ml.), and the separated oil solidified on stirring. Small quantities of unchanged phenylurea were removed by heating the mechanically stirred mixture to 60°, allowing it to cool spontaneously to 40°, and filtering it (filtrate A). The insoluble crude material (12—14 g., 40—54%) was crystallized by treating its boiling ethanolic solution (80 ml.) with charcoal, filtering, and diluting the nearly colourless filtrate with water (20 ml.). On cooling, large colourless lustrous plates of benzenesulphonylphenylcyanamide separated, m. p. 64—66° [Found: C, 60·2, 60·2; H, 4·2, 4·1; N, 11·0, 10·9; S, 11·9, 11·8; *M* (Rast), 256, 266. Calc. for $C_{13}H_{10}O_2N_2S$: C, 60·5; H, 3·9; N, 10·85; S, 12·4%; *M*, 258], not depressed in admixture with material prepared according to v. Braun's method (*loc. cit.*). Varying quantities of sodium benzenesulphonate were isolated from filtrate A after removal of the pyridine by ether-extraction, addition of alkali, and evaporation to small bulk.

(b) *From phenylcyanamide.* A solution of phenylcyanamide (5·5 g.; 0·05 mol.) in pyridine (40 ml.) was treated with benzenesulphonyl chloride (17·6 g.; 14 c.c., 0·1 mol.), heated on the steam-bath for 1 hour, and poured into ice-water (250 ml.); the separated brown oil solidified on standing and gave, on purification with carbon and crystallization from ethanol–water, benzenesulphonylphenylcyanamide (7·8 g., 60%), m. p. 64—66° (Found: C, 60·1; H, 4·1%). Mixed m. p. with material prepared by method (a): 63—66°.

Benzenesulphonylphenylcyanamide and all substituted sulphonylcyanamides subsequently described are highly soluble in cold chloroform, benzene, and acetic anhydride, hot ethanol and acetone; soluble in hot, and sparingly soluble in cold ether and light petroleum; and insoluble in alkalis and water.

*Toluene-*p*-sulphonylphenylcyanamide.*—(a) *From phenylurea.* Phenylurea (27·2 g.; 0·2 mol.), when dissolved in pyridine (100 ml.) and treated with toluene-*p*-sulphonyl chloride (57 g.; 0·3 mol.) as described above, gave a product (22 g.; 40%), which on recrystallization from aqueous ethanol gave lustrous platelets of *toluene-*p*-sulphonylphenylcyanamide*, m. p. 85—87° [Found: C, 61·5, 61·9; H, 4·5, 4·2; N, 10·5, 10·1; S, 11·4, 11·3; *M* (Rast), 260, 268. $C_{14}H_{12}O_2N_2S$ requires C, 61·8; H, 4·4; N, 10·3; S, 11·8%; *M*, 272]. The yield can be raised by the use of a greater excess of sulphonyl chloride (see table). Interaction of the specified quantities of reactants for 6, 3, and 1 hour at room temperature, and 1 hour at 100°, resulted in the formation of 6, 12, 15, and 1% of the theoretical yield, respectively, accompanied by varying quantities of uncrystallizable oily products in the last case.

Mols. of $C_6H_4Me \cdot SO_2Cl$ per mol. of arylurea ...	½	1	2	3	4	5	6
Yield of sulphonyl-cyanamide, % from phenylurea	5	24	41	52	74	90	95
Yield of sulphonyl-cyanamide, % from *p*-tolylurea	6	22	50	72	86	92	93

(b) *From phenylcyanamide.* Phenylcyanamide (5·5 g.; 0·05 mol.), was heated with toluene-*p*-sulphonyl chloride (19·0 g.; 0·1 mol.) to 100° for 1 hour. When the mixture was poured into ice-water (300 ml.) the crude product separated and gave, after purification and crystallization from aqueous ethanol, toluene-*p*-sulphonylphenylcyanamide, m. p. 85—87° (Found: C, 61·8; H, 4·3%). Mixed m. p. with material prepared by method (a): 84—87°.

Toluene-*p*-sulphonylphenylcyanamide (1 g.), dissolved in pyridine (12 ml.) and heated to 100° for 2 hours, was recovered quantitatively.

Hydrolysis to Substituted Sulphonamides.—Into a solution of toluene-*p*-sulphonylphenylcyanamide (5 g.) in ethanol (100 ml.)–benzene (10 ml.), ammonia was passed until the concentration in the liquid corresponded to 3% of ammonium hydroxide (w/v, determined acidimetrically). The clear solution was allowed to stand at room temperature for 24 hours, and evaporated to 15 ml. On neutralization with a few drops of hydrochloric acid and further standing, a white solid separated out which gave, on crystallization from ethanol–light petroleum (b. p. 60—80°), a crystalline mass of toluene-*p*-sulphonamide,

m. p. 137—138°, undepressed in admixture with authentic material From the mother-liquors toluene-*p*-sulphonanilide, m. p. 102—103°, was isolated.

Hydrolysis to Substituted Ureas.—(a) *In alkaline medium.* A solution of toluene-*p*-sulphonylphenylcyanamide (13·6 g.; 0·05 mol.) in alcoholic potassium hydroxide [from 11·2 g. (0·2 mol.) of alkali in 10 ml. of water and 120 ml. of ethanol] was heated under reflux on the steam-bath for 2 hours. The solution, which remained colourless and water-clear during the heating, was nearly neutralized by the addition of concentrated hydrochloric acid (25 ml.) and concentrated to approx. 40 ml. under reduced pressure. On treatment of the residue with water (200 ml.) an oil separated which failed to solidify on standing at 0° for 48 hours. The reaction mixture, again made strongly alkaline (30 ml. of 35% potassium hydroxide), was exhaustively extracted with hot ether (aqueous phase: A), the ethereal extract washed till nearly neutral with water, evaporated in a vacuum, and the oily residue taken up in ethanol. On prolonged standing at 0°, large lustrous prisms of phenylurea crystallized; m. p. 144—147° (3·4 g.; 50%) (Found: C, 61·5; H, 5·7. Calc. for $C_7H_8ON_2$: C, 61·8; H, 5·9%), undepressed in admixture with authentic material. The mother-liquors gave an uncrystallizable oil (1 g.) which was not identified. The aqueous phase A was concentrated to 100 ml., and just neutralized with concentrated hydrochloric acid. On standing, white needles (1·05 g.) separated and gave, on crystallization from ethanol–light petroleum (b. p. 60—80°), toluene-*p*-sulphonanilide, m. p. 102—103° (8·5% of theoretical) (Found: C, 63·4; H, 5·3. Calc. for $C_{13}H_{13}O_2NS$: C, 63·2; H, 5·3%), undepressed in admixture with authentic material. Further evaporation of the aqueous phase A gave varying quantities of sodium toluene-*p*-sulphonate.

(b) *In acid medium.* Toluene-*p*-sulphonylphenylcyanamide, when heated with acetic anhydride or acetic anhydride–pyridine at 100° for 3 hours, was recovered unchanged. A solution of the cyanamide (5·4 g.) in acetic anhydride (40 ml.) was heated under reflux for 5 hours, and the resulting colourless liquid cooled and slowly stirred into ice-water (200 ml.). The separated oil solidified when the whole mixture was shaken with ether (20 ml.), and was filtered off (filtrate: A). The solid (1·9 g.; melting between 130° and 200°) gave toluene-*p*-sulphonanilide, m. p. 101—102°, by extraction with sodium hydroxide solution and reprecipitation with acid. The alkali-insoluble portion was diphenylurea, m. p. 236—238° (Found: C, 73·7; H, 5·4. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7%). The filtrate A contained a small quantity of oil in suspension, which proved to be unchanged starting material.

p-*Nitrobenzenesulphonylphenylcyanamide.*—To a solution of phenylurea (2·8 g.; 0·02 mol.) in pyridine (30 ml.), *p*-nitrobenzenesulphonyl chloride (8·8 g.; 0·04 mol.) was added in one portion, and the temperature kept below 35° by external cooling. Isolation as previously described, and two crystallizations from acetone–ethanol (15 and 25 ml., respectively), gave long, pale yellow needles (4 g.; 66%) of the *cyanamide*, m. p. 147—149° (Found: C, 51·2; H, 3·25; N, 13·4. $C_{13}H_9O_4N_3S$ requires C, 51·5; H, 3·0; N, 13·9%). In a separate experiment the above quantities of reactants were allowed to interact in the smallest possible volume of solvent (12 ml.) (maximum temperature reached: 45°) and the resulting viscous yellow liquid was cooled to 0° for ½ hour. The separated pyridinium *p*-nitrobenzenesulphonate which was highly soluble in water, was filtered off (filtrate A), and identified by conversion (*via* the sulphonyl chloride) into *p*-nitrobenzenesulphonamide, m. p. 178—179°. Filtrate A was worked up as above and gave a 25% yield of *p*-nitrobenzenesulphonylphenylcyanamide, m. p. 147—148°.

Benzenesulphonyl-p-*tolylcyanamide.*—This cyanamide, obtained by addition of benzenesulphonyl chloride (26·4 g.; 20 ml., 0·15 mol.) to a solution of *p*-tolylurea (7·5 g.; 0·05 mol.) in pyridine (50 ml.) in 72% yield, formed large lustrous needles, m. p. 91—93°, from ethanol (Found: C, 61·5; H, 4·75. Calc. for $C_{14}H_{12}O_2N_2S$: C, 61·8; H, 4·4%); not depressed on admixture with material (m. p. 89—91°) prepared according to v. Braun (*loc. cit.*), who reports m. p. 88°.

Toluene-p-*sulphonyl*-p-*tolylcyanamide* resulted in 75% yield from toluene-*p*-sulphonyl chloride (28·5 g.; 0·15 mol.) and *p*-tolylurea (7·5 g.; 0·05 mol.); it formed flat plates, m. p. 124—126°, from ethanol (Found: C, 62·5; H, 5·1. $C_{15}H_{14}O_2N_2S$ requires C, 62·9; H, 4·9%).

Benzenesulphonyl-*p*-methoxyphenylcyanamide was prepared by the interaction of *p*-methoxyphenylurea (8·3 g.; 0·05 mol.) and benzenesulphonyl chloride (17·5 g.; 0·1 mol.) in pyridine (40 ml.). Isolation of the crude material as previously described, and crystallization from aqueous ethanol, gave long colourless lustrous needles, m. p. 102—103° (Found: C, 58·25, 58·1; H, 4·1, 4·1. Calc. for $C_{14}H_{12}O_3N_2S$: C, 58·3; H, 4·2%).

Toluene-p-*sulphonyl*-p-*methoxyphenylcyanamide* resulted from the interaction of *p*-methoxyphenylurea (8·3 g.; 0·05 mol.) and toluene-*p*-sulphonyl chloride (19 g.; 0·1 mol.) in pyridine (40 ml.) and formed colourless lustrous platelets, m. p. 117—118° [Found: C, 59·75; H, 4·65; N, 8·95; S, 10·0; *M* (Rast), 300. $C_{15}H_{14}O_3N_2S$ requires C, 59·6; H, 4·6; N, 9·3; S, 10·6%; *M*, 302].

Toluene-p-*sulphonyltoluene*-p-*sulphonyloxyphenylcyanamide.*—A solution of *p*-hydroxyphenylurea (3 g.; 0·02 mol.) in pyridine (50 ml.) was treated with toluene-*p*-sulphonyl chloride (11·4 g.; 0·06 mol.) with external cooling, and the mixture was kept at 30° for 6 hours. On pouring into ice-water (350 ml.), the oily product first separating out solidified (5·9 g.; 67%) and gave, on four crystallizations from acetone–ethanol–water (3 : 5 : 1), lustrous needles of the *cyanamide*, m. p. 171—173° (Found: C, 57·0; H, 4·2; N, 6·4. $C_{21}H_{18}O_5N_2S_2$ requires C, 57·0; H, 4·1; N, 6·3%).

Benzenesulphonyl-1-*naphthylcyanamide.*—A suspension of 1-naphthylurea (9·3 g.; 0·05 mol.) in pyridine (60 ml.) was treated with benzenesulphonyl chloride (17·6 g.; 14 ml.; 0·1 mol.) below 30°. After 15 minutes' standing, the clear yellow liquid was poured into ice-water, and the oily product solidified on short standing. The mechanically stirred mixture was heated to 60°, and the crude product filtered off. From the filtrate unchanged 1-naphthylurea (1·3 g.; m. p. 224—225°) separated overnight. Two crystallizations of the crude *cyanamide* (8 g.; 52%) from acetone–ethanol (20 and 50 ml., respectively) gave colourless minute needles, m. p. 144—146° (Found: C, 66·3; H, 3·9. $C_{17}H_{12}O_2N_2S$ requires C, 66·2; H, 3·9%).

Toluene-p-*sulphonyl*-1-*naphthylcyanamide* was similarly prepared from 1-naphthylurea (9·3 g.; 0·05 mol.) and toluene-*p*-sulphonyl chloride (19 g.; 0·1 mol.) in 56% yield, and crystallized in lustrous needles, m. p. 156—157° (Found: C, 67·1; H, 4·0. $C_{18}H_{14}O_2N_2S$ requires C, 67·1; H, 4·35%).

p-Nitrobenzenesulphonyl-1-naphthylcyanamide resulted from the interaction of 1-naphthylurea (4·7 g.; 0·025 mol.) and *p*-nitrobenzenesulphonyl chloride (11·1 g.; 0·05 mol.) and formed pale yellow needles, m. p. 177—178°, from acetone–ethanol (Found: C, 57·6; H, 3·3. $C_{17}H_{11}O_4N_3S$ requires C, 57·8; H, 3·1%).

The writer is greatly indebted to Prof. H. Burton for encouragement and valuable advice throughout this investigation.

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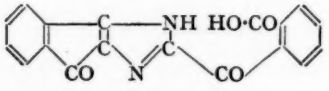
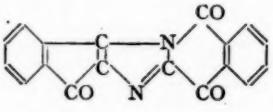
NOTES.

Studies on Indene Derivatives. Part VI. Some New Derivatives of Triketoindane Hydrate ("Ninhydrin"). By RADWAN MOUBASHER.

RUHEMANN (*J.*, 1910, **97**, 1447), by the action of aqueous ammonia on ninhydrin (VIII), obtained a scarlet substance, believed to be 2-*o*-carboxybenzoylindonoglyoxaline (I). This substance, when heated alone or with glacial acetic acid or acetic anhydride, gives a red compound, possibly (II), but structures (III) and (IV) are possible instead of (I) and (II). The acid (I) or (III) reacts with diazomethane giving the *methyl* ester.

(I.) 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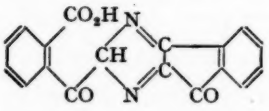
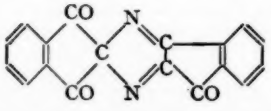
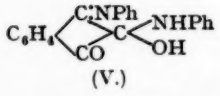
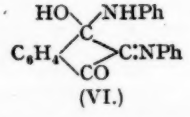
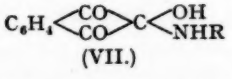
(III.) 


(IV.)

Ninhydrin (VIII) condensed with aniline to give an orange *product* (Ruhemann, *loc. cit.*), but this was not analysed; it could have structure (V) or (VI). *p*-Aminobenzoic acid and *p*-aminophenol react with

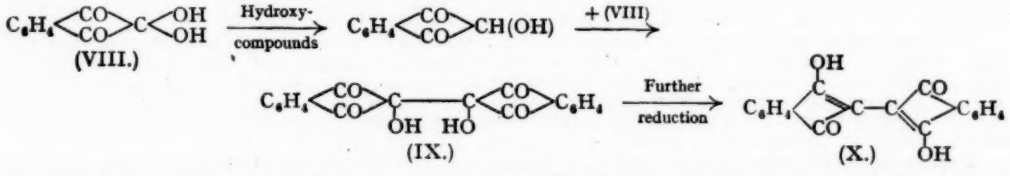

(V.)


(VI.)


(VII.)

ninhydrin to form 2-p-*carboxy*- and 2-p-*hydroxy-anilino*-2-*hydroxy*-1 : 3-*diketoindane* (VII; R = $C_6H_4{\cdot}CO_2H$ and R = $C_6H_4{\cdot}OH$, respectively). This reaction is similar to that of *peri*naphthindane-1 : 2 : 3-trione hydrate with amines (Moubasher and Mostafa, *J.*, 1947, 130).

Ninhydrin when treated with certain hydroxy-compounds (*e.g.*, glycerol, ethylene glycol, or some sugars) gives a characteristic violet coloration (Hall, Loewenstein, and Pribrim, *Biochem. Z.*, 1913, **55**, 357), hydrindantin (IX) * being an intermediate product. The mechanism of this reaction has not yet been explained, but the violet coloration is due to bis-1 : 3-diketoindanyl (enol form) (X), which has been isolated from the mixture.



(VIII.) (IX.) (X.)

Hydrindantin when heated in a vacuum yields (X), and in presence of selenium and oxygen it gives phthalic anhydride.

To ninhydrin, freshly crystallised (0·5 g.), dissolved in hot water (25 c.c.), and cooled; excess of aqueous ammonia was added; a violet solution was obtained, and after 5 minutes at room temperature this was filtered and acidified with concentrated hydrochloric acid. The resulting red gelatinous precipitate of the glyoxaline (I) was filtered off, washed with hot water, dried, and crystallised from alcohol, forming scarlet prisms (0·3 g.); at *ca.* 250° these change to an orange solid, and melt at 345° (brown-red melt).

* For alternative (dihydrated) formula, see Schönberg and Moubasher, *J.*, 1949, 212.

The glyoxaline is soluble in cold aqueous ammonia and is reprecipitated by acids (Found: C, 67·8; H, 2·7; N, 8·6. Calc. for $C_{18}H_{10}O_4N_2$: C, 67·9; H, 3·1; N, 8·8%).

When 0·2 g. of powdered (I) was suspended in dry ether (20 c.c.) and treated with excess of ethereal diazomethane (prepared according to Arndt and Amende, *Z. angew. Chem.*, 1930, **45**, 444), a vigorous reaction took place at room temperature. The mixture was left overnight, and the red precipitate was filtered off and recrystallised from methyl alcohol, forming red needles (0·2 g.), m. p. 245° (red-violet melt), insoluble in alkali but soluble in hot acetic acid, benzene, and alcohols (Found: C, 68·5; H, 3·6; N, 8·4. $C_{19}H_{12}O_4N_2$ requires C, 68·1; H, 3·2; N, 8·1%). The methyl ester gives an orange colour with concentrated sulphuric acid.

The *anhydride* of (I) was prepared by boiling 0·2 g. with acetic anhydride (50 c.c.) or glacial acetic acid (100 c.c.) for 10 minutes. On cooling, a crystalline orange deposit was formed; this was filtered off and crystallised from glacial acetic acid in orange needles (0·18 g.), m. p. 345° (red melt), insoluble in cold or hot ammonia solution and unchanged when refluxed with alcoholic potassium hydroxide (Found: C, 71·8; H, 2·6; N, 9·3. $C_{18}H_8O_3N_2$ requires C, 72·0; H, 2·6; N, 9·3%). It gives an orange-red coloration with concentrated sulphuric acid. The same substance can also be obtained when (I) is heated in a vacuum at 350° (bath temp.)/4 mm.

Action of Aniline on Ninhydrin.—Ninhydrin, freshly crystallised (0·6 g.), was dissolved in water (30 c.c.), and freshly distilled aniline (0·6 g.) was added in portions at room temperature, with shaking. A violet solution was obtained, giving an orange crystalline substance, which was filtered off, washed with water, and recrystallised from 50% aqueous alcohol; orange needles (0·8 g.) were formed, m. p. 99° (decomp.), depending on rate of heating (Found: C, 76·9; H, 4·8; N, 8·5. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·7; N, 8·5%).

When this compound (V or VI) (0·5 g.) was boiled for 5 minutes with concentrated hydrochloric acid (15 c.c.), a yellow solution was obtained. This was cooled and extracted several times with small amounts of ether. The combined ethereal solutions were evaporated to dryness. The residue formed colourless crystals of ninhydrin (m. p., mixed m. p., and colour reactions). The aqueous layer contained aniline hydrochloride (formation of benzeneazo-β-naphthol).

Action of p-*Aminobenzoic Acid on Ninhydrin.*—Ninhydrin (1 g.) was dissolved in hot benzene (50 c.c.), and a hot benzene solution of *p*-aminobenzoic acid (1·5 g. in 50 c.c.) added. The mixture was heated under reflux for 3 hours; a deep violet coloration was immediately observed, which changed to orange, and an orange precipitate began to form. After cooling, this was filtered off, and when recrystallised from ethyl alcohol afforded orange needles (1·6 g.), m. p. 230° (decomp.; brown melt) (Found: C, 64·8; H, 3·7; N, 4·8. $C_{16}H_{11}O_5N$ requires C, 64·6; H, 3·7; N, 4·7%). The substance (VII; $R = C_6H_4{\cdot}CO_2H$) is soluble in alkali and in alcohols, giving red solutions, but difficultly soluble in ether; with sodium hydrogen carbonate solution it evolves carbon dioxide and gives a red solution.

When this product (0·5 g.) was treated with 18N-sulphuric acid (20 c.c.), the colour disappeared immediately; after 10 minutes at room temperature the mixture was heated on a steam-bath for 3 minutes, then cooled and diluted with water (50 c.c.); a colourless solid separated and was proved to be *p*-aminobenzoic acid (m. p. and mixed m. p.), and the solution contained ninhydrin (extracted with ether and identified by m. p., mixed m. p., and properties).

Action of p-*Aminophenol on Ninhydrin.*—Ninhydrin (0·5 g.), dissolved in acetic acid (20 c.c.), and *p*-aminophenol (0·7 g.), dissolved in acetic acid (50 c.c.), were heated together on a steam-bath for 30 minutes; on concentration and cooling, a precipitate was formed, and after separation this crystallised from absolute methyl alcohol in dark reddish crystals (0·2 g.), m. p. 210° (decomp.) (Found: N, 5·0. $C_{15}H_{11}O_4N$ requires N, 5·2%). These gave a beautiful red coloration with concentrated sulphuric acid, and an intense blue with sodium hydroxide solution.

Action of Hydroxy-compounds on Hydrindantin.—Hydrindantin (0·5 g.) was treated with 95% ethyl alcohol (100 c.c.), *iso*propyl alcohol (50 c.c.), glycerol (50 c.c., mixed with 50 c.c. of water), or glucose (2 g. in 100 c.c. of water) and heated under reflux for about 3 hours; the colour gradually became red then intensely violet, and a violet precipitate was formed; after dilution with water, this was filtered off, dried, and recrystallised from benzene, forming violet needles, m. p. 297° (decomp.), of bis-1 : 3-diketoindanyl (m. p., and mixed m. p., and properties). The yield in all these cases was about 80%.

Action of Heat on Hydrindantin.—(a) *In a vacuum* (experiment by William Awad). 0·5 G. of hydrindantin was placed in a pyrolysis flask and heated in a vacuum (10 mm.) at 280—300° (bath temp.) for ½ hour; violet crystals were formed on the cold parts of the flask, and after recrystallisation from benzene, these were identified as bis-1 : 3-diketoindanyl (m. p., 297°, mixed m. p., and pink colour with sulphuric acid).

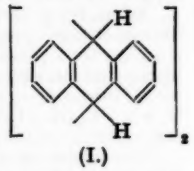
(b) *In presence of selenium and oxygen.* 0·5 G. of hydrindantin was mixed with powdered selenium (Kahlbaum; 4 g.), placed in a dry test-tube, and heated in a metal-bath at 290° for an hour, a current of oxygen being passed through the tube. The colourless sublimate formed was returned to the tube, and the heating repeated for 10 minutes. The colourless needles formed on the cold parts of the tube were proved to be phthalic anhydride (m. p., 131°, and mixed m. p.).—Fouad I University, Faculty of Science, Cairo, Egypt. [*Received, July 24th*, 1948.]

Photochemical Reactions. Part XIV. The Action of Sunlight on Some Carcinogenic Hydrocarbons.

By Alexander Schönberg and Ahmed Mustafa.

Previously (*J.*, 1948, 2126), we showed that 1 : 2-benzanthracene, which is closely related to substances showing strong carcinogenic action, forms a photo-dimer under the influence of sunlight. We now find that 5-methyl-1 : 2-benzanthracene, 20-methylcholanthrene, and 4′-methyl-1 : 2-benzanthracene [of which the first two are strongly carcinogenic (Cook, Robinson, and Goulden, *J.*, 1937, 393; Cook and Haslewood, *J.*, 1934, 430)] similarly form polymers, which, by analogy with dianthracene (I), are

believed to be dimeric and to have a constitution similar to (I). These photo-products are colourless or nearly so, and regenerate the monomers under the influence of heat, thus behaving like (I).



(I.)

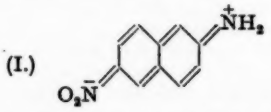
To our previous discussion (*loc. cit.*) of the possible connexion between carcinogenicity and photo-activity, we now add the conception that photo-activated (biologically highly active) compounds may be produced within the body if normal biochemical reactions are accompanied by chemi-luminescence.

Polymerisations.—5-Methyl-1 : 2-benzanthracene, dissolved in benzene, was exposed in a sealed "Monax" tube (filled with CO_2) to the action of sunlight during 15 days (November); the colourless *photo-dimer* which separated was washed several times with hot benzene to remove the unchanged material and then melted at about 185° (Found: C, 94·3; H, 5·7. $C_{38}H_{28}$ requires C, 94·2; H, 5·8%). 4-Methyl-1 : 2-benzanthracene similarly gave a colourless *photo-dimer*, m. p. about 230° (Found: C, 94·2; H, 5·7%). 20-Methylcholanthrene, in benzene, was exposed as described above in a "Pyrex" tube for 30 days (December—January). The almost colourless *photo-dimer* was washed with hot benzene (in which it was difficultly soluble) and crystallised from a large amount of xylene; it was insoluble in aqueous potassium hydroxide and melted between 295° and 305° (Found: C, 94·1; H, 5·9. $C_{42}H_{32}$ requires C, 94·0; H, 6·0%).

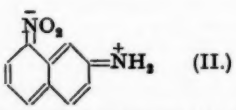
Action of Heat.—The photo-dimers were heated for 30 minutes in a stream of CO_2; in all cases a crystalline sublimate of the respective monomer was obtained and identified by m. p. and mixed m. p. Bath-temperatures used were: 20-methylcholanthrene, 360°; 5- and 4′-methyl-1 : 2-benzanthracene, 270°.—FACULTY OF SCIENCE, FOUAD I UNIVERSITY, ABBASSIA, CAIRO. [*Received, July 10th*, 1948.]

The Separation of 6- and 8-Nitro-2-naphthylamine. By HERBERT H. HODGSON and JOHN RATCLIFFE.

6- AND 8-NITRO-2-NAPHTHYLAMINE can resonate into the quinonoid structures (I) and (II), of which (I) is by far the more stable and makes a greater contribution to its resonance hybrid. In consequence the 8-nitro- will be more basic than the 6-nitro-isomeride, and a separation is now reported from their mixture which depends on this property, *viz.*, the prior solubility of the 8-nitro-2-naphthylamine in very dilute hydrochloric acid; this appears to be more complete and much less tedious than the fractional crystallisation processes of previous workers (cf. Veselý and Jakes, *Bull. Soc. chim.*, 1923, **33**, 942; Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **52**, 638).



(I.)



(II.)

Experimental.—The mixture (140 g.) of 1-, 6-, and 8-nitroaceto-2-naphthalides, obtained by nitration of the acet-β-naphthalide from β-naphthylamine (120 g.) *via* the procedure of Hartman and Smith (*Org. Synth.*, Coll. Vol. II, p. 438) or that of Saunders and Hamilton (*loc. cit.*), was refluxed for 20 minutes with benzene (800 c.c.), and the mixture cooled to 40° and filtered. The filtrate afforded the 1-nitroaceto-2-naphthalide (70—75 g.), while the insoluble portion (50—55 g., m. p. 140—150°), which contained approximately equal amounts of the three isomerides, was refluxed for 1 hour with a solution of ethanol (200 c.c.) and hydrochloric acid (50 c.c., *d* 1·18), and filtered hot. The deposit *A*, which had formed during the reflux period, was almost exclusively a mixture of 6- and 8-nitro-2-naphthylamine hydrochlorides, but at room temperature the further deposit *B* contained, in addition, substantial amounts of the 1-nitro-isomeride. On addition of water to the filtrate from *B*, the precipitate *C* (13 g.) was mainly the 1-nitro- with a little of the 6-nitro-2-naphthylamine. The final filtrate when rendered alkaline with ammonia, gave a precipitate *D*, which consisted mainly of 8-nitro-2-naphthylamine contaminated with a small amount of an unidentified impurity. 8-Nitro-2-naphthylamine was removed completely from the precipitates *A*, *B*, and *D* by several extractions with cold dilute hydrochloric acid (containing 1 c.c. of acid, *d* 1·18, per 100 c.c. of water), *ca.* 6 l. being used in all. The combined filtrates, when just basified with ammonia, at 0°, afforded micro-crystals of almost pure 8-nitro-2-naphthylamine (10—12 g.), m. p. 98—102°, which crystallised from ethanol in red needles, m. p. 104·5—105° (lit., m. p. 103·5°). The residues from *A* and *B*, together with *C*, were extracted by boiling ethanol (100 c.c.), and the extract cooled rapidly and filtered before crystallisation began; the insoluble 6-nitro-2-naphthylamine (10—12 g., m. p. 203—205°) crystallised from ethanol in thin yellow-orange plates, m. p. 207—207·5° (lit., m. p. 203°). The hot filtrate (above) deposited 1-nitro-2-naphthylamine, which crystallised from ethanol in thick red needles, m. p. 126—127°. The approximate ratio now obtained of 1 : 1 for the amounts of the 6- and the 8-nitro-2-naphthylamine, agrees with that of Veselý and Jakes (*loc. cit.*) but differs from the 1 : 3 ratio reported by Saunders and Hamilton (*loc. cit.*).—TECHNICAL COLLEGE, HUDDERSFIELD. TECHNICAL COLLEGE OF SOUTH-EAST ESSEX, DAGENHAM. [*Received, October 1st*, 1948.]

A Synthesis of DL-*Valine from Ethyl Acetamidomalonate.* By R. O. ATKINSON and P. A. A. SCOTT.

VALINE has been prepared by the Strecker (Lipp, *Annalen*, 1880, **205**, 9, 18) and halogen-acid (*Org. Synth.*, 1940, **20**, 106) methods, and by a variation of the Sörensen method, namely the reaction of *iso*propyl iodide with ethyl benzamidomalonate (Redeman and Dunn, *J. Biol. Chem.*, 1939, **130**, 346). Its preparation by the reaction of *iso*propyl bromide with ethyl acetamidocyanoacetate (Albertson and Tuller, *J. Amer. Chem. Soc.*, 1945, **67**, 502) has been claimed.

It has been reported by Snyder, Shekleton, and Lewis (*J. Amer. Chem. Soc.*, 1945, **67**, 310) that attempts to prepare *iso*leucine and valine by alkylation of ethyl acetamidomalonate with *sec.*-butyl bromide and *iso*propyl bromide, respectively, were unsuccessful, and they suggested that secondary halides are of little use in this or any of the variations of the Sörensen method.

We have found this to be the case for *sec.*-butyl bromide, but we have prepared valine by this method in 31·5% overall yield. The alkylation proceeds very slowly, and a reaction period of 72 hours is necessary for maximum yield. This time, however, can be halved by using the corresponding iodide.

Experimental.—*Ethyl α-acetamido-α-carbethoxyisovalerate.* To a solution of sodium (23 g.) in specially-dried ethyl alcohol (1500 ml.) ethyl acetamidomalonate (217 g.; 1 mole) was added. *iso*Propyl bromide (123 g.; 1 mole) was added to the resultant solution with stirring. The mixture was boiled under reflux for 72 hours, and the alcohol was then removed by distillation. The product was extracted from the residue with ether, and the extract concentrated to a pale brown syrup which crystallised on cooling to give ethyl α-acetamido-α-carbethoxy*iso*valerate (92 g.; 37%), m. p. 73° (uncorr.) (Found: C, 55·4; H, 8·14; N, 5·32. Calc. for $C_{12}H_{21}O_5N$: C, 55·6; H, 8·17; N, 5·40%).

DL-*Valine.*—A mixture of ethyl α-acetamido-α-carbethoxy*iso*valerate (50 g.) and 48% hydrobromic acid (250 ml.) was heated under reflux for 18 hours. The hydrobromic acid was then removed by distillation under reduced pressure, and the residue was dissolved in water, treated with charcoal, and filtered. The filtrate was adjusted to pH 6 with ammonia, and an equal volume of methanol was added. The mixture was chilled overnight, and valine filtered off, washed free of bromide with methanol, and recrystallised from aqueous alcohol (yield, 20 g.; 85%) (Found: N, 11·8. Calc. for $C_5H_{11}O_2N$: N, 11·9%).

We wish to thank the Board of Directors of the British Drug Houses Ltd., for permission to publish this note.—AMINO ACIDS DEPARTMENT, THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, August 12th*, 1948.]

The Structure and Reactivity of Free Radicals.

THE TILDEN LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY ON NOVEMBER 11TH, 1948.

By C. E. H. BAWN, Ph.D.

ONE of the outstanding achievements of the study of chemical kinetics has been the demonstration that many apparently complex chemical changes occur in a sequence of stages, each of which is characterised by extreme simplicity. Many of these are chain reactions involving atoms or radicals formed by the breaking of chemical bonds, and experiment has shown that the various stages in the chain are the most elementary types of reaction involving the transfer of an electron or an atom from one reactant to the other.

The thermal decomposition and oxidation of hydrocarbons, or the formation and breakdown of addition polymers, are typical of reactions which involve the participation of intermediary free radicals. The initiation of these processes by the formation of an atom or radical sets in motion the sequence of elementary reactions which lead to the final stable products. It is evident that the complete unravelling of this sequence, and the formulation of the rates and energy changes of the simple reactions which make up the complete picture, would not only enable us to predict quantitatively the course and rate of any change, but would also constitute the basis of a theory of chemical reactivity. Recent progress in the study of radical reaction has taken us some way towards this goal. It is with these general principles of radical reactions rather than the detailed consideration of any particular class of chain-reaction that I wish to deal.

The characteristic property of a free radical is that it carries an unpaired electron, and this electron is available for the formation of a bond with another radical, or atom or group of a molecule. This immediately gives us a convenient classification of radical reactions: (*a*) inter-radical reactions, and (*b*) reactions of radicals with molecules.

Inter-radical Reactions.

When two radicals come together, alternative reaction possibilities exist. Either they combine together to give a saturated molecule, or an atom transfer occurs with the formation of a saturated and an unsaturated molecule, *e.g.*:

$$C_2H_5 + C_2H_5 \longrightarrow C_4H_{10} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$\longrightarrow C_2H_6 + C_2H_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Reactions of this type are those which lead to the destruction of radicals and are chain-terminating processes. It is because they are usually the terminating process of a reaction sequence that it has been a matter of some difficulty to decide experimentally the relative probabilities of (1) and (2) and to specify the rates of these processes. Recently, by the use of the technique of highly attenuated flames (Polanyi, " Atomic Reactions," Williams and Norgate, 1932; Bawn, *Ann. Reports*, 1942, **39**, 36), it has been possible to prepare radicals in a relatively pure state, free from reactive partners, and to study the kinetics of these simple reactions.

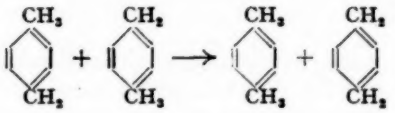
Under these conditions (in the temperature range 280—380°) it has been found that, with alkyl radicals, disproportionation is a relatively easy process and requires little or no activation (Bawn and Tipper, Faraday Soc. Discussion, " Labile Molecules," 1947, p. 104) *e.g.*:

$$CH_3 + CH_3 \longrightarrow CH_4 + CH_2. \quad E = 8 \text{ k.-cals.}$$
$$C_2H_5 + C_2H_5 \longrightarrow C_2H_6 + C_2H_4. \quad E = \sim 0 \text{ k.-cals.}$$
$$C_3H_7 + C_3H_7 \longrightarrow C_3H_8 + C_3H_6. \quad E = \sim 0 \quad ,,$$

These conclusions are strongly supported by the corresponding reactions in solution. By studying the reactions of radicals prepared by the dissociation of silver alkyls (−60° to 0°) (Bawn and Whitby, *ibid.*, p. 228), $AgCH_3 \longrightarrow Ag + CH_3$, and $AgC_2H_5 \longrightarrow Ag + C_2H_5$, it has been shown that methyl radicals recombine entirely to give ethane, whereas ethyl radicals largely disproportionate. Under the same conditions of preparation, both radicals initiate the polymerisation of vinyl acetate.

In thermal reactions, disproportionation is invariably accompanied by extensive recombination, and the activation energies of the above reactions are evaluated on the assumption that the activation energy for recombination is zero. The latter value has not been measured directly for simple radicals, and various values for E have been assigned to this reaction. The weight of evidence is now in favour of $E_{\text{recomb.}} = 0$ for simple alkyl radicals. It has been frequently stated that, since methyl is planar whilst in ethane the structure is tetrahedral, the transition which occurs when the radicals join up would require an appreciable activation energy. Calculation, however, shows that attraction between the two free carbon orbitals in flat methyl, even at relatively large distances, is greater than the H–H repulsions. The flat radicals thus attract each other at large distances, and the hydrogens slip over to the tetrahedral configuration without activation.

The corresponding reactions between simple aryl radicals are particularly interesting since, with one notable exception, dimerisation seems to proceed exclusively. For example, in investigations of highly attenuated flames, phenyl, benzyl, and benzoyl give dimers, and recently Szwarc and his collaborators (*J. Chem. Physics*, 1948, **16**, 128, 981) have shown by thermal-decomposition studies that *o*- and *m*-xylyl radicals and the fluoro-*o*-, -*m*-, and -*p*-tolyl radicals dimerise. The exception is *p*-xylyl which disproportionates to give a biradical:



The reason for this will be considered later.

Thermal Stability.—In any thermal reaction there is superimposed upon the effects of recombination and disproportionation the tendency of the radicals to decompose. Thus the tendency of the alkyl radicals to split up into a radical and an olefin increases with increase in chain length. A consideration of this factor leads to an interesting series of radical stabilities. The dissociation of methyl according to $CH_3 \longrightarrow CH_2 + H$ requires energy of the order of the C–H bond strength in methyl and is variously estimated as 80—95 k.-cals. Thus methyl should be stable up to 1000°, in agreement with experiment. With the ethyl radical the corresponding process can occur much more easily, since an unsaturated structure is produced with the corresponding liberation of energy equivalent to the second half of the double bond: $C_2H_5 \longrightarrow C_2H_4 + H - 42$ k.-cals.

A different process occurs with the propyl and higher radicals, since now it is the weaker C–C bond which is broken. The dissociation to form methyl, $CH_3{\cdot}CH_2{\cdot}CH_2 \longrightarrow CH_3 + CH_2{:}CH_2 - 33$ k.-cals., is much easier on thermochemical grounds than is the reaction, $CH_3{\cdot}CH_2{\cdot}CH_2 \longrightarrow CH_3{\cdot}CH{:}CH_2 + H - 42$ k.-cals. The *iso*propyl radicals decompose similarly, the unsaturated molecule being formed by the simultaneous movement of a hydrogen atom during the dissociation, and as a consequence may have a slightly higher dissociation energy. For these simple radicals the order of stability is, therefore, Me > Et > Pr^i > Pr^n. Butyl differs from the propyl radical in that an ethyl may be formed instead of a methyl radical: $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2 \longrightarrow CH_3{\cdot}CH_2 + CH_2{:}CH_2$. In contrast with methyl, ethyl radicals and those higher in the series are stabilised by resonance. For the ethyl radical we may write structure (I), or any of the three equivalent structures (II). There are also ionic structures which are much less stable than (I) and (II) and make only a very small contribution to the resonance energy. Structure (I) is much favoured energetically and the free valency resides

largely on the end carbon atom. The small probability of three structures of type (II), however, results in increased stability of the radical, and the effect increases in the series: Et < Pr < Pr^i < Bu^t. Table I summarises the calculated resonance energies of these radicals (Baughan, Evans, and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 377).

In view of the marked increase in radical stability in passing from CH_3 to C_2H_5, the butyl radical will decompose preferentially into C_2H_5 and ethylene. Furthermore, since the

TABLE I.

Calculated resonance energy of radicals.

Radical.	Me.	Et.	Pr^n.	Pr^i.	Bu^n.	Bu^i.	Bu^t.
No. of resonating structures ...	0	3	3	6	3	3	9
Resonance energy	0	7·1	8·6	14·1	(9·5)	10·2	21·1

undissociated propyl and butyl radicals have approximately the same resonance stability, it follows that the butyl radical will be less stable than propyl:

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2 \longrightarrow CH_3 + CH_2{:}CH{\cdot}CH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\longrightarrow C_2H_5 + CH_2{:}CH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The relative rates of the alternative reactions (3) and (4) cannot be calculated directly from the energies of the processes, but it is reasonable to assume that the stabilisation in the transition state will follow that of the radical. Thus if the activation energy difference of (3) and (4) is 2 k.-cals., the rate of (4) will be three times that of (3) at 600°.

If the following dissociation reactions of the C_3- and C_4-radicals

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot} \longrightarrow CH_3 + CH_2{:}CH_2$$

$$\begin{matrix} & CH_3 & \\ & \diagdown & \\ & \cdot C{-}H & \\ & \diagup & \\ & CH_3 & \end{matrix} \longrightarrow CH_3 + CH_2{:}CH_2$$

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot} \longrightarrow CH_3 + CH_3{\cdot}CH{:}CH_2$$

$$\begin{matrix} CH_3 & & H & & \\ & \diagdown & \diagup & & \\ & & C{-}CH_2{\cdot} & & \\ & \diagup & & & \\ CH_3 & & & & \end{matrix} \longrightarrow CH_3 + CH_3{\cdot}CH{:}CH_2$$

$$\begin{matrix} & CH_3 & \\ & \diagdown & \\ CH_3{-}C{\cdot} & & \\ & \diagup & \\ & CH_3 & \end{matrix} \longrightarrow CH_3 + CH_3{\cdot}CH{:}CH_2$$

give methyl and an unsaturated molecule are compared, it follows from the data given in Table I that the relative stabilities of the radicals in this reaction can be arranged in the following order, the stability decreasing from left to right: Pr^n > Pr^i; Bu^t > Bu^i > Bu^n.

Similar reasoning may be applied to the C_5- and higher radicals, each of which shows alternative paths of decomposition, the most probable being that determined by the relative resonance stabilisation of the initial and product radicals. As pointed out by Kossiakoff and Rice (*J. Amer. Chem. Soc.*, 1943, **65**, 590), with the long chain radical it is possible that the chain can coil round to produce a more stable isomer. For example, the following equilibrium may be established with hexyl:

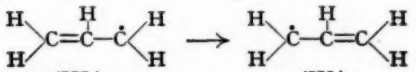
$$\begin{matrix} CH_3 & & & \\ CH_2 & & CH_2 & \\ H{-}C{-}H & & CH_2 & \\ CH_3 & & & \end{matrix} \rightleftharpoons \begin{matrix} & & CH_3 & \\ & \diagup & & \diagdown \\ CH_2 & & & CH_2 \\ \cdot CH & & & CH_3 \\ & \diagdown & & \\ & & CH_3 & \end{matrix}$$

The possibility also exists that the radical will shed a methyl group with the formation of a 5-membered ring.

In our previous considerations we have dealt with " saturated " radicals in which, in spite of the possibility of excited structures contributing to the stability of the normal form of the radical, the free electron resides predominantly on a single carbon atom. There is only a small chance of its being found on the hydrogens of the methyl or methylene group, but this is sufficient to modify bond energies and reactivities.

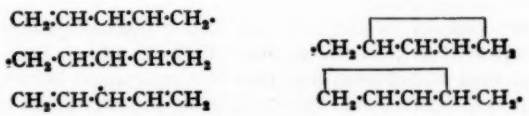
A different situation is encountered with " unsaturated " radicals, and the free valency may

be shared among several atoms. Thus in the allyl radical structures (III) and (IV) are equally important:



(III.) (IV.)

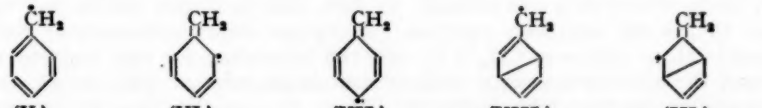
The free valency can now be regarded as being equally distributed between the two end carbon atoms, which will therefore be equally reactive. Similar considerations apply to other aliphatic unsaturated radicals of the general structure, $C_{2n+1}H_{2n+3}$. Thus the radical C_5H_7 will have the following five unexcited structures:



Quantum mechanical calculations (Coulson and Moffitt, *Trans. Faraday Soc.*, 1948, **44**, 81) show that the free valency is roughly evenly distributed between the odd-indexed carbon atoms with slightly greater probability for the end carbons. The free bond is zero at the even indexed carbons. This new development of the calculation of the electronic constitution of free radicals thus provides a quantitative measure of the reactivity of the different positions of the chain. The occurrence of resonance also confers a very marked stability on the radical. Thus the resonance energies of the radicals C_3H_5 and C_5H_7, discussed above are 18·7 and 30·4 k.-cals., respectively.

Much more attention has been paid to the theory of the stability of aromatic radicals, probably for two reasons: (*a*) because of the impact of the early work of Gomberg on the triphenylmethyl type radicals, and (*b*) because they constitute an ideal conjugated system much more amenable to theoretical treatment than are saturated radicals.

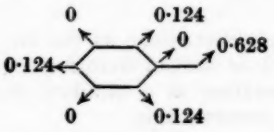
The benzyl radical may be selected as an illustration. The structures (V)—(IX) correspond to the different ways of pairing of the π electrons, the · denoting in each structure the single unpaired electron:



(V.) (2 Structures) (VI.) (2 Structures) (VII.) (VIII.) (3 Structures) (IX.) (2 Structures)

As before, the radical is considerably stabilised, and the values of the resonance energy additional to that of the parent hydrocarbon for a few simple aromatic hydrocarbons are shown in Table III (*q.v.*).

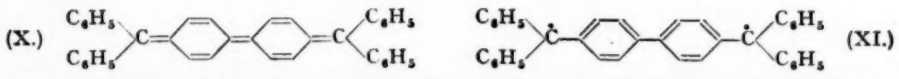
Recent theoretical developments (Coulson, Faraday Soc. Discussion, "Labile Molecules," 1947, p. 9) have also made possible the assignment of numerical values for the absolute reactivity of different positions of the molecule. The typical result for the free valency at different positions of the benzyl radical derived by the molecular orbital method is shown below:



Biradicals.—In the disproportionation reaction of both methyl and *p*-xylyl radicals considered above, methylene and ·CH_2—C$_6$H$_4$—CH_2· were postulated as intermediate products. Whereas a monoradical can be defined unambiguously as possessing one unpaired electron and therefore is paramagnetic, with the above radicals the question immediately arises—are they biradicals having two unpaired electrons, or do the bonds rearrange to give molecules? If the energy

levels of the molecule and radical are sufficiently close together, then the distinction between the biradical and molecular state will not be very sharp.

The question is not new; the problem whether molecules of the Chichibabin hydrocarbon type, *e.g.*,



should be assigned a quinonoid structure (X) or a benzenoid radical structure (XI) has been frequently discussed. The question in terms of molecular-orbital theory reduces to one of the magnitude of excitation from the singlet (all electrons paired) to the triplet state (two unpaired electrons). If this value is sufficiently small, excited molecules may be present in equilibrium even at low temperature.

The energy and free valency of the molecule and biradical quinodimethane have recently been calculated by Coulson *et al.* (*loc. cit.*, p. 36), who have shown that the resonance energy of the molecule is close to that of benzene, and that the separation between the ground state and the triplet state is such that there would be a negligible concentration of radicals in equilibrium with molecules at room temperature. The free valency at the end carbon atoms is unusually high—almost the same as that of the benzyl radical—and very little lower than that of the triplet state. This explains the high reactivity at these carbon atoms. The argument, often used, that the high reactivity of large aromatic molecules implies a biradical structure can now be stated alternatively by saying that certain carbon atoms (*e.g.*, in rubrene) have a high concentration of free valency (detailed calculations on the energy of the triplet state for some 93 polyene and aromatic hydrocarbons have been made by Diatkina and Syrkin (*Acta Physicochim. U.R.S.S.*, 1946, **21**, 23).

Whereas application of the quantum theory to aromatic radicals has been particularly successful, its application to even the simplest aliphatic radicals has been somewhat disappointing. Our theoretical knowledge of methylene is not nearly so complete as that of quinodimethane and there exists a marked difference of opinion as to whether the ground state of methylene is singlet or triplet. A study of the reaction, $^{-}CH_2Br + Na \longrightarrow NaBr + CH_2$, which has been discussed in detail elsewhere (Bawn and Dunning, *Trans. Faraday Soc.*, 1939, **35**, 185) provides extremely strong evidence that the luminescence emitted can result only from the formation of CH_2 in a singlet state. The high reactivity claimed for methylene is not sufficient evidence to justify its existence as a free radical. In fact, kinetic studies (Bawn and Tipper, *loc. cit.*) show that CH_2 is not extremely reactive. Methylene disproportionates at 300° according to the scheme, $CH_2 + CH_2 \longrightarrow CH_4 + C$, and the activation for this reaction is 14·0 k.-cals. greater than the activation energy of the dimerisation reaction, $CH_2 + CH_2 \longrightarrow C_2H_4$. The direct association reaction with hydrogen, $CH_2 + H_2 \longrightarrow CH_4$, has an activation energy of 13·5 k.-cals.

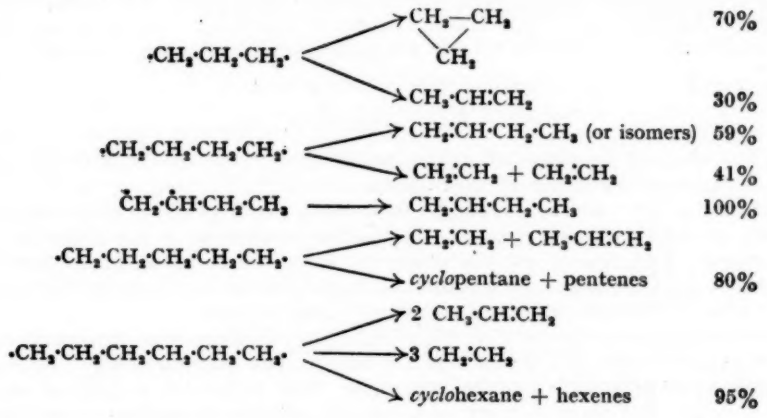
The higher biradicals of the form $R—CH_2—CH<$ have not been identified in thermal processes. An attempt to prepare ethylidene from a saturated molecule $CH_3{\cdot}C\langle^{H}_{X}{}^{X}$ or the radical $CH_3{\cdot}\dot{C}\langle^{H}_{X}$ would involve the breaking of one or both C—X bonds, and this process would be much easier if accompanied by the simultaneous formation of a double bond. Thus the reaction:

$$CH_2—\dot{C}HBr + Na \longrightarrow CH_2—C\langle^{H} \longrightarrow C_2H_4 + NaBr,$$

when carried out in hydrogen, gives ethylene as the only product. No ethane is formed as would be expected if the ethylidene radical were formed. The direct opening of the double bond in $CH_2{:}CHX$ with the formation of a biradical does occur in the thermal and photal initiation of polymerisation and isomerisation.

In contrast to methylene, dimethylene, and ethylidene, the higher homologues from trimethylene to hexamethylene are produced, in sodium-atom reactions, in the biradical state. With these radicals no quino-type structure exists and the possibility of the pairing of the single electrons formed at the end of a chain of methylene is extremely remote. The experimental results can be most satisfactorily explained if an intermediate and reactive biradical is formed, which undergoes either cyclisation or re-arrangement, with or without dissociation to unsaturated molecules. The analytical results at 300° are summarised in the following table.

It is interesting that there seems to be a minimum of stability in the series $[CH_2]_n$ at $n = 4$, and that this is in agreement with greater ease of formation and the stability of 5- and 6-membered rings.



Reactions of Radicals with Hydrocarbons.

So far we have been concerned only with the stability of simple radicals and with the reactions involving them alone. However, except in very special experimental circumstances, the radical is formed in the presence of other molecules which are usually in an overwhelming concentration compared with that of the radical itself; *e.g.*, in thermal reactions or in polymerisation in liquid systems, the concentration of radicals is usually 10^{-4}—10^{-9} molar. The natural tendency of the radicals to saturate themselves is the source of their marked reactivity, and this tendency is, as expected, dependent on the structure of both the radical and the reacting molecule. It is evident from the above considerations that relative probabilities of attack of an alkyl radical on a hydrocarbon would be greater at a tertiary than at a secondary, and that in turn greater than at a primary carbon atom. This is completely borne out by the direct measurements of Taylor *et al.* (*J. Chem. Physics*, 1939, **7**, 390; 1940, **8**, 396) (Tables II and III), by data on the

TABLE II.

Reaction of methyl radicals with aliphatic hydrocarbons.

Reaction.	Activation energy, k.-cals.	C–H bond strength, k.-cals.	Resonance energy of radical, k.-cals.
$CH_3 + C_2H_6$	8·3	97·5	7·1
C_3H_8	5·5	95·0	8·6
n-C_4H_{10}	5·5	94·0	(9)
iso-C_4H_{10}	4·2	86·0	10·2
*neo*Pentane	8·3	—	(7)

thermal decomposition of hydrocarbons and by the chain-transfer process in polymerisation (*q.v.*). It has been shown from kinetic studies that primary < secondary < tertiary is the order of decreasing C–H bond strength. The lower activation energies with butane and *iso*butane may be ascribed to the greater reactivity of secondary and tertiary hydrogens, which in turn is due to the greater resonance stabilities of the radicals formed. The similarity of the value for ethane and *neo*pentane indicates that the removal of the primary hydrogen atom is independent of the hydrocarbon and that both of the radicals formed will have similar stability.

TABLE III.

Reaction of methyl radicals with aromatic hydrocarbons.

Reaction.	Activation energy, k.-cals.	Resonance energy of radical (β = 20 k.-cals.), k.-cals.
$CH_3 + C_6H_6$	10	0
$C_6H_5{\cdot}CH_3$	5·6	14·4
$C_6H_5{\cdot}CH_2{\cdot}C_6H_5$	5·6	26·0

The corresponding studies with aromatic hydrocarbons are not so complete, but the relatively low values for toluene and diphenylmethane (Table III) indicate side-chain attack with the formation of very stable radicals.

It follows, of course, that the greater the resonance stabilisation of a radical the less will be its tendency to capture a hydrogen from a saturated molecule. Thus, in any reaction of a radical R_1 with a hydrocarbon RH to give a new radical R, the energy change is given by:

$$R_1 + RH \longrightarrow R_1H + R$$
$$\Delta H = D_{R_1H} - D_{RH} + R_R - R_{R_1}$$

where D_{R_1H} and D_{RH} are the dissociation energies of the C–H bonds in R_1H and RH, and R_{R_1} and R_R are the resonance energies of the radicals.

It is evident that for a series of aliphatic R_1 radicals reacting with a given hydrocarbon RH the variation of activation will parallel the radical stabilities of the aliphatic radicals R_1 previously given. The reason for the preferred dimerisation of aromatic radicals such as $C_6H_5\cdot CH_2\cdot$ and $C_6H_5\cdot CO\cdot$, even in the presence of a large excess of hydrocarbon, is now understandable in view of the high resonance stability of these radicals.

Many interesting questions arise as to the attack of free radicals on unsaturated hydrocarbons. These will be taken up later and it will suffice to refer to two examples only. Both methyl and propyl radicals react very rapidly with propylene, their respective activation energies being 3·1 and 4·5 k.-cals. The corresponding reaction with ethylene is negligible and indicates that the seat of reaction is not at the double bond, but at the methyl group. This is associated with the resonance characteristics of the allyl radical formed.

$$CH_3\cdot + CH_3\cdot CH{:}CH_2 \longrightarrow CH_4 + \dot{C}H_2\cdot CH{:}CH_2$$
$$CH_3\cdot CH_2\cdot \dot{C}H_2 + CH_3\cdot CH{:}CH_2 \longrightarrow CH_3\cdot CH_2\cdot CH_3 + \dot{C}H_2\cdot CH{:}CH_2$$

These are examples of the principle established by the work of Farmer (*Trans. Faraday Soc.*, 1942, **38**, 348) and others that the attack of free radicals on non-conjugated olefinic systems takes place at the α-methylene group. The allylic radical formed is stabilised to the extent of 18—20 k.-cals. The stabilisation is greatly increased in 1 : 3- and 1 : 4-dienes, the former of which gives the radical, $CH_2{:}CH\cdot CH{:}CH\cdot CH_2\cdot$, which has a resonance energy of 30 k.-cals.

Addition Polymerisation.—A most important development in free-radical chemistry has taken place in recent years in the study of vinyl polymerisations. There is no doubt whatever that thermal, photochemical, and certain types of catalysed polymerisation proceed by a free-radical mechanism. In fact the study of poly-reactions has proved to be a most useful and powerful method for the investigation of radical reactions. Some of these results will now be briefly summarised.

The fundamental reaction in the chain polymerisation is the interaction of a radical with the double bond of the polymerising monomer to give a larger free radical. This process continues until the radical is destroyed and the chain terminated.

$$\cdot R + CH_2{:}CHX \longrightarrow R\cdot CH_2\cdot \dot{C}HX$$
$$R\cdot CH_2\cdot \dot{C}HX + CH_2{:}CHX \longrightarrow R'\cdot CH_2\cdot \dot{C}HX, \text{ etc.}$$

The termination of the chain requires destruction of the growing radical. The simplest types of reaction are those by which two radicals mutually destroy each other either by combination or disproportionation:

$$R\cdot CH_2\cdot \dot{C}HX + R\cdot CH_2\cdot \dot{C}HX \longrightarrow R\cdot [CH_2\cdot CHX]_2\cdot R$$
$$R\cdot CH_2\cdot \dot{C}HX + R\cdot CH_2\cdot \dot{C}HX \longrightarrow R\cdot CH_2\cdot CH_2X + R\cdot CH{:}CHX,$$

the second process requiring hydrogen transfer.

Disproportionation is the more common reaction leading to cessation and only in one case—the OH-radical-catalysed polymerisation of methyl methacrylate (Baxendale, Evans, and Kilham, *Trans. Faraday Soc.*, 1946, **42**, 668)—has a recombination mechanism been definitely established.

The few measurements which have as yet been made of the disproportion reaction show that the chain ends have little difficulty in colliding and reacting, and that the activation energy of the process is zero or at most a few k.-cals.

The difficulty of polymerising monomers with α-methylene hydrogen atoms by a free radical mechanism is well known. Thus propylene, *iso*butene, *iso*octene, and allyl acetate give only

products of low molecular weight, and this is undoubtedly due to the ready capture of an α-methylenic hydrogen atom by the polymer radical, to give the stable allylic-type radical; *e.g.*,

$$X{\cdot}CH_2{\cdot}CH{:}CH_2 + R \longrightarrow X{\cdot}CH_2{\cdot}CHR{\cdot}\dot{C}H_2 \text{ (Initiation)}$$
$$X{\cdot}CH_2{\cdot}CHR{\cdot}\dot{C}H_2 + X{\cdot}CH_2{\cdot}CH{:}CH_2 \longrightarrow X{\cdot}CH_2{\cdot}CHR{\cdot}CH_2 + \dot{C}HX{\cdot}CH{:}CH_2$$

On the other hand, the typical α-methyl-containing monomers such as methacrylate or methacrylonitrile polymerise easily to high-molecular products because substitution stabilises the propagating radical and α-methylenic abstraction is greatly reduced. Similarly, the highly stable styrene-type radical, $Ph{\cdot}\dot{C}H{\cdot}CH_2X$, shows little tendency to transfer. In fact, it may be concluded quite generally that substitutents effective in promoting radical stabilisation greatly reduce the probability of monomer chain-transfer.

In solution polymerisation, the solvent may also take part in transfer in a manner analogous to that of monomer transfer discussed above. The activity of the radical may be transferred to the solvent, forming a new radical which may start a fresh chain:

$$\cdot M_n + SH \longrightarrow M_n + S\cdot$$
$$\cdot S + M \longrightarrow M\cdot + HS \text{ or } SM\cdot$$

Mayo has shown (Mayo, *J. Amer. Chem. Soc.*, 1943, **65**, 2324; Gregg and Mayo, Faraday Soc. Discussion, "Labile Molecule," 1947, p. 328) that, if all the new radicals S· start chains, a simple relation exists between the average degree of polymerisation $\bar{P}$ and the chain-transfer coefficient C, viz.,

$$\frac{1}{\bar{P}} = \frac{1}{\bar{P}_0} + C\frac{[SH]}{[M]}$$

where $C = k_s/k_p$ is the ratio of the velocity constant of the reaction, $M_n\cdot + S \xrightarrow[k_s]{} M_n + S\cdot$, to that of the reaction, $M_n\cdot + M \xrightarrow[k_p]{} \dot{M}_{n+1}$, and $\bar{P}_0$ is the average degree of polymerisation in absence of the chain-transfer agent. The chain-transfer coefficient is thus a comparison of the reactivity of the growing polymer radical for reaction with the solvent and with that of the monomer. By using a variety of chain-transfer agents in the same polymeric system it is thus possible to compare the absolute velocities of reaction of a given polymer radical with a series of solvent molecules. Mayo (*loc. cit.*) has shown, from transfer measurements on the styrene radical in a series of hydrocarbons (that is, a measurement of the capacity to supply a hydrogen atom to a substituted benzyl radical), that the ease with which the hydrogen atom can be removed from a carbon atom in methane is increased appreciably by alkyl groups on the carbon atom, greatly by phenyl groups, and still more by an *o*-diphenylene group (fluorene being 1000 times more reactive than *cyclo*hexane). These results show that the increased activity in chain transfer with hydrocarbons is determined by the stability of the solvent-type radical formed, the least activation energy being required to form the most stable radical.

Copolymerisation.—When the material undergoing polymerisation consists of a mixture of two unsaturated monomers, the addition polymer formed is built up from units of each of the monomers. Such a polymer is known as a copolymer. In these mixtures the rate of polymerisation by a radical mechanism is governed by four chain-growth processes, determined by the two types of radical reacting with M_1 and M_2, *viz.*: $M_1\cdot + M_1 \xrightarrow{k_{11}} M_1\cdot$; $M_1\cdot + M_2 \xrightarrow{k_{12}} M_2\cdot$; $M_2\cdot + M_2 \xrightarrow{k_{22}} M_2\cdot$; $M_2\cdot + M_1 \xrightarrow{k_{21}} M_1\cdot$. By the use of the stationary-state method it is possible to derive the copolymerisation equation:

$$\frac{dM_1}{dM_2} = \frac{M_1 r_1 M_1 + M_2}{M_2 r_2 M_2 + M_1}$$

where $r_1 = k_{11}/k_{12}$, and $r_2 = k_{22}/k_{21}$. The equation can be intergrated and from a knowledge of the experimentally determined monomer ratio in the polymer, together with a knowledge of the initial composition of the mixture, the reactivity ratios, r_1 and r_2, can be determined.

Now, the reactivity ratios are the ratios of the rate of addition of a monomer to a radical of its own kind and that of the rate of addition of the second monomer to the same radical. This ratio supplies, therefore, a quantitative measure of the rate of reaction of any radical with another monomer. A monomer reactivity ratio >1 indicates a tendency of the radical to perpetuate its own kind, whilst a ratio <1 indicates a preference for reaction with the other monomer. Thus the relative rate constants of the reactivity of a reference radical with a number of monomers can be determined. Table IV (Mayo, Lewis, and Walling, Faraday Soc. Discussion, "Labile

TABLE IV.

	r_1.	r_2.		r_1.	r_2.
Styrene	1·00	1·00	Vinyl chloride	17	0·02
Butadiene	0·78	—	Vinyl acetate	55	0·01
Methyl methacrylate	0·52	0·46	Vinyl ethyl ether	90	—
Methyl vinyl ketone	0·29	—	Allyl chloride	31	—
Acrylonitrile	0·40	0·04	Allyl acetate	90	0·01
2-Chloroethyl acrylate	0·54	0·10	Maleic anhydride	0·01	0·07
Methyl acrylate	0·75	0·18	Diethyl fumarate	0·30	—
Vinylidene chloride	1·85	0·14	Diethyl maleate	6·52	—
Methallyl chloride	22	—			
Methallyl acetate	71	—			

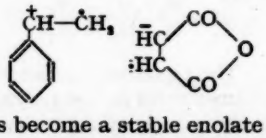
Molecule," 1947, p. 285) shows the relative reactivities of various monomers with the styrene radical. The results, for instance, show that the rate of reaction of the styrene radical with methyl methacrylate is just twice that with styrene momomer, whereas with vinylidene chloride it is about half as fast.

The table shows clearly the specific nature of the reactivity of free radicals. It so happens that the order in which radicals fall is much the same for a number of different radicals, even though the absolute rates may vary greatly from one radical to another. The broad conclusion which follows is that monomers with conjugated vinyl, phenyl, carbonyl, cyano-, or carbalkoxy-groups are considerably more reactive than the monomers without such conjugation. The data show also that the addition of one methyl or one chlorine substituent increases the reactivity of the double bond: methacrylate > acrylate; methacrylonitrile > acrylonitrile; vinylidene chloride > vinyl chloride; methallyl > allyl. It has thus become possible to compile a list (*loc. cit.*) of the ability of substituents R to increase the reactivity of the monomer $CH_2{:}CHR$ towards free radicals, viz., $C_6H_5 > H_2C{:}CH > R{\cdot}CO{\cdot} > N{:}C{\cdot} > RO{\cdot}CO{\cdot} > Br > Cl > R{:}O{\cdot} > R{\cdot}CH_2{\cdot} > H$.

It follows from our previous consideration of resonance stabilisation of radicals that the most reactive double bonds yield the most stabilised and the least reactive radicals, and that the least reactive double bonds yield the most reactive radicals.

The above order of substituents is, therefore, that corresponding to the order of their ability to promote resonance stabilisation of the methyl radical. Thus, $\cdot CH_2{\cdot}CH{:}CH_2$ or $CH_2{\cdot}CH_2{\cdot}C_6H_5$ should be more stabilised and less reactive than $\cdot CH_2Cl$ or $\cdot CH_2{\cdot}CH_2{\cdot}R$, and the free CH_3 should be most reactive. This order agrees with the low reactivity of triphenylmethyl and allyl radicals.

A striking feature of many free radical polymerisations is that, in many pairs, each radical reacts preferentially with the opposite-type radical, giving rise to an alternating effect in the chain. The copolymer formed consists of regularly alternating units of the two polymers, *e.g.*, styrene–maleic anhydride, and styrene–allyl acetate. Maleic anhydride or the maleic esters do not polymerise alone (or with great difficulty to low degrees of polymerisation), but will readily copolymerise with other monomers, such as styrene, and may even accelerate the rate. In many copolymerisations this tendency to alternation is superimposed upon the general activity of monomers in copolymerisation. Two explanations have been advanced to explain the alternation effect. Price (Price, *J. Polymer. Sci.*, 1946, **1** 83; Price and Alfrey, *ibid.*, 1947, **2**, 101) assumed that the effect arises from the difference in polarity of the radical and the double bond, a negative radical being attracted by a positive double bond and vice versa. The other explanation, due to Mayo *et al.* (*loc. cit.*), assumes that special resonance forms are available to the reactants in the transition state, *e.g.*, the double bond of the styrene molecule donates an electron to the maleic anhydride radical, the resulting structures being



The maleic anhydride portion has become a stable enolate ion, and the styrene portion has now available more resonance structures. Reactions of this type introduce a new feature which is of particular interest since electrostatic influences are not usually encountered among free radical reactions. The general effect of electron availability and the effect of substituents on the charge distribution in radicals are not yet understood and must await further experimental and theoretical developments. Nevertheless, it appears that the main features of radical reactions can be interpreted in terms of the resonance energies and the strength of bonds.

for Solvents . . .

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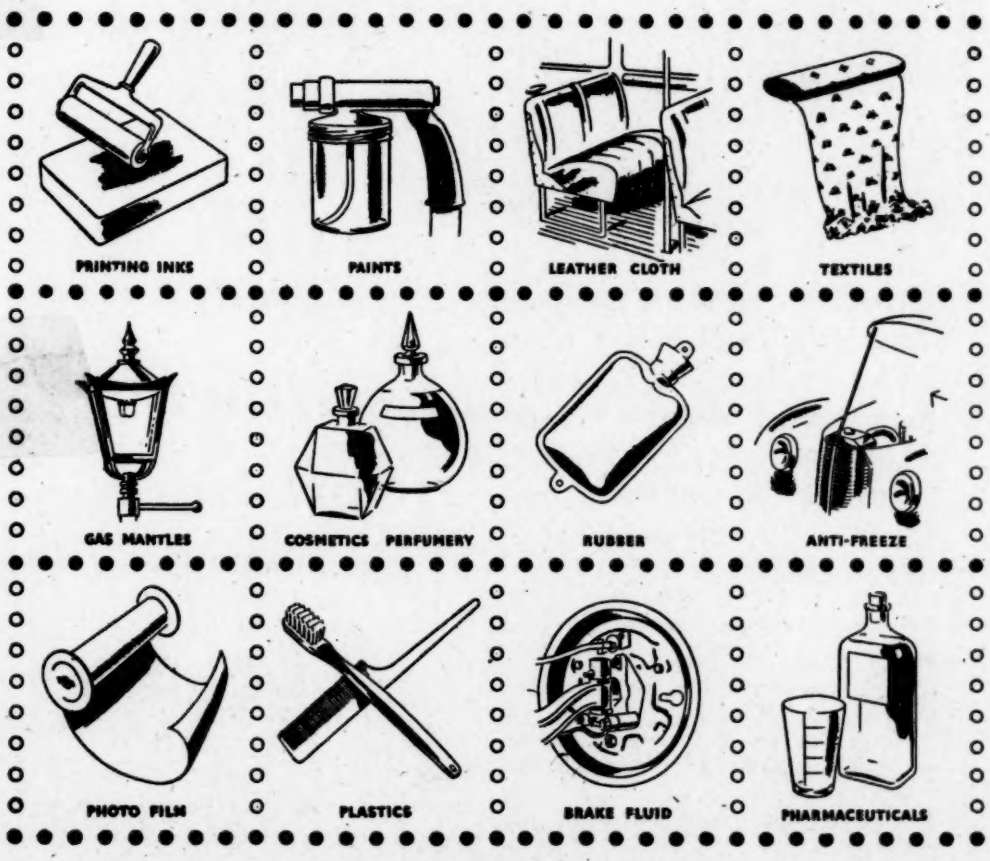

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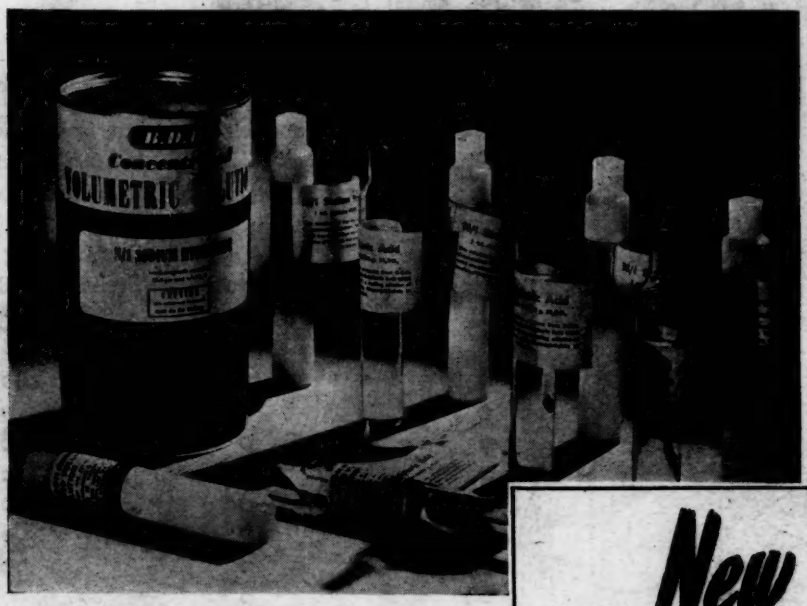

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